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Protocol Version 4 – 03 January 2020
Protocol Version 5 – 20 April 2020

Study Title: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Phase III Study to Evaluate the Efficacy and Safety of Elafibranor in Patients with Nonalcoholic Steatohepatitis (NASH) and fibrosis

Protocol Reference Number: GFT505-315-1

NCT Number: NCT02704403

GENFIT
TOWARDS BETTER MEDICINE

CLINICAL PROTOCOL – PHASE 3

Protocol N° GFT505-315-1

EudraCT N°2015-005385-38

IND number: 115028

Version number: FINAL 1.0 - Release date: January 15 2016

A Multicenter, Randomized, Double-Blind, Placebo-Controlled Phase III Study to Evaluate the Efficacy and Safety of Elafibranor in Patients with Nonalcoholic Steatohepatitis (NASH) and fibrosis

International Coordinating Investigator Committee	[redacted]	[redacted]
Sponsor	**GENFIT**	Parc Eurasanté 885, Avenue Eugène Avinée 59120 LOOS, France
Represented by:	[redacted]	[redacted]

CLINICAL STUDY PROTOCOL SIGNATURE PAGE

Protocol N°: **GFT505-315-1 / EudraCT N° 2015-005385-38/ IND n°115028**

Version number: **1.0**

Release date: **January 15 2016**

TITLE: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Phase III Study to Evaluate the Efficacy and Safety of Elafibranor in Patients with Nonalcoholic Steatohepatitis (NASH) and fibrosis.

In signing below, I give agreement to the protocol.

International Coordinators:

[redacted]

Signature *Date(dd-mmm-yyyy)*

On behalf of (the Sponsor): GENFIT
Parc Eurasanté
885, Avenue Eugène Avinée
59120 LOOS – France

Name: [redacted]

[redacted]

Signature *Date(dd-mmm-yyyy)*

CLINICAL STUDY PROTOCOL

INVESTIGATOR SIGNATURE PAGE

PROTOCOL TITLE: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Phase III Study to Evaluate the Efficacy and Safety of Elafibranor in Patients with Nonalcoholic Steatohepatitis (NASH) and fibrosis.

PROTOCOL NUMBER: GFT505-315-1

EudraCT Number: 2015-005385-38

IND Number: 115028

CLINICAL PHASE: 3

VERSION: 1.0

DATE: January 15, 2016

SPONSOR: GENFIT,
Parc Eurasanté,
885 Avenue Eugène Avinée,
59120 LOOS - France

In signing below, I confirm having read the protocol, and give agreement to the protocol.

INVESTIGATOR NAME: _____

INSTITUTION NAME: _____

INSTITUTION ADDRESS: _____

_____

SIGNATURE: _____

DATE: _____ /_____ /_____

Day Month Year

STUDY CONTACTS

Protocol N°: **GFT505-315-1/ EudraCT N° 2015-005385-38/ IND n° 115028**

International Coordinating Investigator Committee	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]
Pharmacovigilance	[redacted]	[redacted]

IXRS	[redacted]
Study drug supplier	[redacted]
Central laboratory	[redacted]
Central pathology laboratory	[redacted]
ePRO	[redacted]

CLINICAL TRIAL SYNOPSIS

Sponsor:	Study Drug:	Protocol Number:
GENFIT	Elafibranor (GFT505): Propanoic acid, 2-[2,6-dimethyl-4-[3-[4-(methylthio)phenyl]-3-oxo-1(E)-propenyl] phenoxy]-2-methylpropanoic acid	GFT505-315-1

Title of the study:
A Multicenter, Randomized, Double-Blind, Placebo-Controlled Phase III Study to Evaluate the Efficacy and Safety of Elafibranor in Patients with Nonalcoholic Steatohepatitis (NASH) and fibrosis

Phase:
Phase III
Indication:
NASH

Study design and dose levels:
Randomized, double-blind, parallel groups (placebo or elafibranor [GFT505]) placebo-controlled study, evaluating the efficacy and safety of elafibranor 120 mg QD versus placebo in an adult NASH population with fibrosis. The first double-blind 72-week treatment period will assess the efficacy and safety of elafibranor on the resolution of NASH without worsening of fibrosis at the intermediate efficacy analysis, followed by a Long-term Treatment Period to assess efficacy on all-cause mortality and liver-related clinical outcomes as measured by the time to first occurrence of any of the listed adjudicated events (all-cause mortality, progression to histological cirrhosis, and the full list of portal hypertension/cirrhosis related events).
Dose level
120 mg
Route of administration:
Oral (1 tablet once daily [QD])

Primary objectives – surrogate endpoint (at interim analysis)
To evaluate the efficacy of elafibranor QD for 72 weeks versus placebo on resolution of NASH without worsening of fibrosis.

- Resolution of NASH is defined as the disappearance of ballooning and disappearance or persistence of minimal lobular inflammation (grade 0 or 1) with an overall pattern of injury not qualifying for steatohepatitis.
- Worsening of fibrosis is evaluated using the NASH Clinical Research Network (CRN) fibrosis staging system and defined as progression of at least one stage.

Primary objectives – long-term endpoints
To evaluate the efficacy of elafibranor on clinical outcomes described as a composite endpoint composed of death to any cause, liver cirrhosis, and the full list of portal hypertension/cirrhosis related events:

- Liver transplantation
- MELD score ≥15
- HCC
- Hospitalization (as defined by a stay of 24 hours or greater) for new onset or recurrence of:
    - variceal bleed,
    - hepatic encephalopathy,
    - spontaneous bacterial peritonitis,
    - uncontrolled ascites,
    - hepatorenal syndrome,
    - hepatopulmonary syndrome,
    - chronic gastrointestinal blood loss due to portal hypertensive gastropathy (provided that these lead to hospitalization or transfusion).

Key secondary objective (at interim analysis)
To assess histological changes after 72 weeks of treatment on the following endpoint parameter:

- Percentage of patients with improvement of fibrosis of at least 1 stage according to NASH CRN scoring.

Other secondary objectives

- To assess histological changes after 72 weeks of treatment and follow-up biopsy on the following parameters:
  - percentage of patients with resolution of NASH without worsening of fibrosis (follow-up biopsy)
  - percentage of patients with improvement of fibrosis of at least 1 stage according to NASH CRN scoring
  - percentage of patients with at least 1 point improvement in histological scores (NASH CRN scoring: total nonalcoholic fatty liver disease (NAFLD) activity score (NAS), steatosis, hepatic ballooning, lobular inflammation), fibrosis (NAFLD Ishak scoring system), or portal inflammation
  - percentage of patients with improvement of NAS score of at least 2 points.
  - percentage of patients with at least a 1 point improvement in steatosis-activity-fibrosis (SAF) activity score
  - mean changes in NAS score, fibrosis, steatosis, hepatic ballooning, lobular inflammation, portal inflammation, SAF activity score
  - changes in area of fibrosis by morphometry
  - mean changes in fibrosis using NASH CRN and NAFLD Ishak scoring.
- To assess the following endpoints in elafibranor treated patients relative to placebo, at Week 72, and at the end of the Long-term Treatment Period:
  - cardiovascular events
  - liver-related death events
  - changes in liver enzymes and liver markers
  - changes in noninvasive markers of fibrosis and steatosis
  - changes in lipid parameters
  - variation in body weight
  - changes in insulin resistance and glucose homeostasis markers
  - changes in inflammatory markers
  - changes in cardiovascular risk profile as assessed by Framingham scores
  - changes in quality of life (36-Item Short-Form Health Survey [SF-36]) questionnaire)
- To assess Time to first occurrence of:
  - liver cirrhosis
  - death of any cause
  - any portal hypertension or cirrhosis related events.

Exploratory objectives

- To determine pharmacokinetic (PK) parameters of elafibranor (GFT505) and GFT1007 after 72 weeks of treatment for PK population analyses.
- To constitute a biobank for discovery and validation of biomarkers in NASH.

Exploratory objectives for F1 group

- To explore the following endpoints in elafibranor treated F1 patients in the exploratory group relative to placebo at Week 72 and at the end of the Long-term Treatment Period:
  - resolution of NASH without worsening of fibrosis
  - percentage of patients with at least 1 point reduction in NASH CRN fibrosis score and NAFLD Ishak score
  - percentage of patients with at least 1 point improvement in NAS, steatosis, ballooning, lobular inflammation, or portal inflammation
  - percentage of patients with improvement of NAS score of at least 2 points
  - percentage of patients with at least a 1 point improvement in SAF activity score
  - mean changes in NAS score, fibrosis (using NASH CRN or NAFLD Ishak scoring system), steatosis, hepatic ballooning, lobular inflammation, portal inflammation, SAF activity score
  - changes in area of fibrosis by morphometry.
- To explore the following endpoints in F1 patients at Week 72 and after the Long-term Treatment Period:
  - composite long-term endpoints
  - cardiovascular events
  - changes in liver enzymes and liver markers
  - changes in noninvasive markers of fibrosis and steatosis
  - changes in lipid parameters
  - variation in body weight

- changes in insulin resistance and glucose homeostasis markers
- changes in inflammatory markers
- changes in cardiovascular risk profile as assessed by Framingham scores
- changes in quality of life (SF-36 questionnaire).

- To determine PK parameters of elafibranor (GFT505) and GFT1007 after 72 weeks of treatment.
- To assess the tolerability and safety.

Safety secondary objectives

- To assess the tolerability and safety of once a day administration of oral doses of elafibranor 120 mg description of:
  - serious adverse events, adverse events, physical examination, vital signs, medical history, electrocardiogram
  - hematological parameters
  - liver function parameters
  - renal function parameters (including urinalysis)
  - cardiac function parameters
  - metabolic parameters
  - other biochemical safety markers.

Patient population:

NASH diagnosed as:

Steatohepatitis evaluated by a centrally-read liver biopsy taken within 6 months prior to randomization (if no historical biopsy is available for NASH diagnosis, a liver biopsy will be performed during the Screening Period) with:

- At least a score of 1 in each component of the NAS score (steatosis scored 0-3, ballooning degeneration scored 0-2, and lobular inflammation scored 0-3).
- NAS ≥4.
- fibrosis stage of 1 or greater and below 4, according to the NASH CRN fibrosis staging system.
  For patients with fibrosis stage 1, only patients at high risk of progression will be included, meaning with a NAS score ≥5 and 2 of the following conditions: persistent elevated alanine aminotransferase (ALT), obesity defined by a body mass index (BMI) ≥30, metabolic syndrome (NCEP ATP III definition), type 2 diabetes, or homeostasis model assessment of insulin resistance (HOMA-IR) >6.

At the end of the 72-week treatment period, patients will continue in the double-blind Long-term Treatment Period. Patients will be monitored by notably measuring the potential appearance of cirrhosis (based on FibroScan measurement for presence of cirrhosis associated with biological and clinical assessments and confirmed by biopsy). If histological cirrhosis is confirmed as well as any other event listed in the long-term composite endpoint, patients will be discontinued from study.

Number of estimated randomized F2-F3 Patients: total 2022 patients (ratio 2:1)

- 674 patients in placebo group
- 1348 patients in elafibranor (GFT505) group

An additional 202 (10% of the F2-F3 patients) F1 patients at high risk of progression will be included as an exploratory arm.

Number of participating centers (planned): ~200 centers

Number of participating countries: ~20 (Belgium, France, Germany, Italy, the Netherlands, Romania, Spain, UK, Switzerland, Portugal, Denmark, Finland, Sweden, Czech republic, Russia, Turkey, USA, Canada, Colombia, Brazil, Argentina, Chile, Australia, South Africa)

Study duration per patient:

Estimated duration approximately 72 months, based on 456 patients experiencing a long-term composite endpoint event.

Schedule:

- Screening Period: Week-12 to Week -1 prior to randomization.
- First Treatment Period: Week 0 to Week 72: period of treatment with elafibranor (GFT505) or placebo for 72 weeks.
- Long-term Treatment Period: Week 72 to end of study: extension of treatment with elafibranor (GFT505) or placebo (until occurrence of prespecified number of events).

Inclusion criteria:

Patients must meet all of the following inclusion criteria to be eligible for enrollment in the trial:

1. Males or females aged from 18 to 75 years inclusive at first Screening Visit.
2. Must provide signed written informed consent and agree to comply with the study protocol.
3. Body Mass Index ≤45 kg/m².

4. Females participating in the study must either not be of childbearing potential (hysterectomy, bilateral oophorectomy, medically documented ovarian failure, or >50 years of age with cessation of menses for at least 12 months due to ovarian failure) or using efficient double contraception: hormonal contraception (including patch, contraceptive ring, etc), intra-uterine device, or other mechanical contraception method + condom or diaphragm or spermicide for the full duration of the study and for 1 month after the end of treatment.
5. Histological confirmation of steatohepatitis on a diagnostic liver biopsy by central reading of the slides (biopsy obtained within 6 months prior to Randomization or during the Screening Period) with at least 1 in each component of the NAS score (steatosis scored 0-3, ballooning degeneration scored 0-2, and lobular inflammation scored 0-3).
6. NAS score ≥4.
7. Fibrosis stage of 1 or greater and below 4, according to the NASH CRN fibrosis staging system.
   For patients with fibrosis stage 1, only patients at high risk of progression will be included meaning with a NAS score ≥5 and 2 of the following conditions: persistent elevated ALT, obesity defined by a BMI ≥30, metabolic syndrome (NCEP ATP III definition), type 2 diabetes, or HOMA-IR >6.
8. Patients agree to have 1 liver biopsy during the Screening Period for diagnostic purpose (if no historical biopsy within 6 months before Randomization is available), 1 liver biopsy after 72-weeks of treatment for assessment of the treatment effects on NASH, as well as another in case of suspicion of cirrhosis (to have a histological confirmation), and a final liver biopsy after approximately 4 years of treatment (visit V13), unless a biopsy has already been performed within the year.
9. Stable dose of vitamin E (>400 IU/day), polyunsaturated fatty acids (>2 g/day), or ursodeoxycholic acid from at least 6 months prior to diagnostic liver biopsy.
10. For patients with type 2 diabetes, glycemia must be controlled. If glycemia is controlled by antidiabetic drugs, no change in anti-diabetic therapy is allowed within 6 months prior to diagnostic liver biopsy, under the following conditions:
    - no change in dose for patients treated by glucagon-like peptide 1 agonist
    - no qualitative change (i.e. implementation of a new anti-diabetic drug) for patients treated by metformin, dipeptidyl-peptidase 4 inhibitors, sodium/glucose cotransporter 2 inhibitors, sulfamides, or insulin.

Exclusion criteria:

Patients who meet any of the following criteria will be excluded from entering the study:

1. Known heart failure (Grade I to IV of New York Heart Association classification).
2. History of efficient bariatric surgery within 5 years prior to Screening.
3. Uncontrolled hypertension during the Screening Period despite optimal antihypertensive therapy.
4. Type 1 diabetes patients.
5. Patients with decompensated diabetes (hemoglobin A1c [HbA1c] >9.0%). If abnormal at the first Screening Visit, the HbA1c measurement can be repeated at the latest 2 weeks prior to Randomization. A repeated abnormal HbA1c (HbA1c >9.0%) leads to exclusion.
6. Patients receiving thiazoledinediones (pioglitazone, rosiglitazone), unless the drug was discontinued at least 6 months before the diagnostic liver biopsy.
7. Patients with a history of clinically significant acute cardiac event within 6 months prior to Screening such as: acute cardiovascular episode, stroke, transient ischemic attack, or coronary heart disease (angina pectoris, myocardial infarction, revascularization procedures).
8. Weight loss of more than 5% within 6 months prior to Randomization.
9. Compensated and decompensated cirrhosis (clinical and/or histological evidence of cirrhosis). Notably, NASH patients with fibrosis stage = 4 according to the NASH CRN fibrosis staging system are excluded.
10. Current or recent history (<5 years) of significant alcohol Consumption. For men, significant consumption is typically defined as higher than 30 g pure alcohol per day. For women, it is typically defined as higher than 20 g pure alcohol per day.
11. Patients who have donated blood or blood products within 1 month prior to Screening or who plan to donate blood or blood products at any time during the trial and in the 2 months following the end of the study.
12. Pregnant or lactating females or females planning to become pregnant during the study period.
13. Other well documented causes of chronic liver disease according to standard diagnostic procedures including, but not restricted to:
    - positive hepatitis B surface antigen
    - positive hepatitis C Virus RNA)

- suspicion of drug-induced liver disease
- alcoholic liver disease
- autoimmune hepatitis
- Wilson's disease hemochromatosis
- primary biliary cirrhosis, primary sclerosing cholangitis
- genetic hemochromatosis
- known or suspected HCC
- history or planned liver transplant, or current MELD score >12

14. Where applicable, patients not covered by Health Insurance System and/or not in compliance with the recommendations of National Law in force.
15. Patients who cannot be contacted in case of emergency.
16. Known hypersensitivity to the investigation product or any of its formulation excipients.
17. Patients with previous exposure to elafibranor.
18. Patients who are currently participating in, plan to participate in, or have participated in an investigational drug or medical device trial within 30 days or five half-lives, whichever is longer, prior to Screening.

Concomitant medications:

19. Fibrates are not permitted from 2 months before Randomization. Patients that used statins or ezetimibe before Screening may participate if the dosage has been kept constant for at least 2 months prior to Screening.
20. Currently taking drugs that can induce steatosis/steatohepatitis including, but not restricted to: corticosteroids (parenteral & oral chronic administration only), amiodarone (Cordarone), tamoxifen (Nolvadex), and methotrexate (Rheumatrex, Trexall), which are not permitted 30 days prior to Screening.
21. Currently taking any medication that could interfere with study medication absorption, distribution, metabolism, or excretion or could lead to induction or inhibition of microsomal enzymes, e.g. indomethacin, which are not permitted from Randomization.

Associated illnesses or conditions:

22. Any medical conditions that may diminish life expectancy to less than 2 years including known cancers.
23. Evidence of any other unstable or, untreated clinically significant immunological, endocrine, hematological, gastrointestinal, neurological, neoplastic or psychiatric disease.
24. Mental instability or incompetence, such that the validity of informed consent or ability to be compliant with the study is uncertain.

In addition to the above criteria, patient should not present any of the following biological exclusion criteria:

25. Positive anti-human immunodeficiency virus antibody.
26. Aspartate aminotransferase (AST) and/or ALT >10 x the upper limit normal (ULN).
27. Total bilirubin >25 µmol/L (1.5 mg/dL).
28. International normalized ratio >1.4.
29. platelet count <100,000/mm^3.
30. Serum creatinine levels >135 µmol/L (>1.53 mg/dL) in males and >110 µmol/L (>1.24 mg/dL) in females.
31. Significant renal disease, including nephritic syndrome, chronic kidney disease (defined as patients with markers of kidney damage or estimated glomerular filtration rate [eGFR] of less than 60 ml/min/1.73 m^2). If abnormal at the first Screening Visit, the eGFR measurement can be repeated prior to the Randomization within the following timeframe: minimum 4 weeks after initial test and maximum 2 weeks prior to planned Randomization. A repeated abnormal eGFR (less than 60 ml/min/1.73 m^2) leads to exclusion.
32. Unexplained serum creatine phosphokinase (CPK) >3 x the ULN. In case of explained elevated CPK >3 x the ULN, the measurement can be repeated prior to Randomization. In this case, retest should be performed within 1 to 2 weeks after initial test. A CPK retest >3 x ULN leads to exclusion.

Criteria for Evaluation:

Primary endpoint

Surrogate endpoint - resolution of NASH (at interim analysis)

The resolution of NASH without worsening of fibrosis after 72 weeks of treatment with elafibranor.

Long-term endpoint – time to clinical event/death

To evaluate the efficacy of elafibranor on clinical outcomes described as a composite endpoint composed of death to any cause, liver cirrhosis and the full list of portal hypertension/cirrhosis related events:

- liver transplantation
- MELD score ≥15
- HCC
- hospitalization (as defined by a stay of 24 hours or greater) for new onset or recurrence of:
    - variceal bleed
    - hepatic encephalopathy
    - spontaneous bacterial peritonitis
    - uncontrolled ascites, hepatorenal syndrome
    - hepatopulmonary syndrome
    - chronic gastrointestinal blood loss due to portal hypertensive gastropathy (provided that these lead to hospitalization or transfusion).

The final analysis will be performed when 456 patients experience an event listed above. This is expected to occur approximately 72 months after the first patient is randomized.

Key secondary endpoint (at interim analysis)

Percentage of patients with improvement of fibrosis of at least 1 stage according to NASH CRN scoring at 72 weeks.

Other secondary endpoints

- To assess histological changes after 72 weeks of treatment and follow-up biopsy on the following parameters:
    - percentage of patients with resolution of NASH without worsening of fibrosis (follow-up biopsy)
    - percentage of patients with improvement of fibrosis of at least 1 stage according to NASH CRN scoring
    - percentage of patients with at least 1 point improvement in histological scores (NASH CRN scoring: total NAS, steatosis, hepatic ballooning, lobular inflammation), fibrosis (NAFLD Ishak scoring system), or portal inflammation
    - percentage of patients improvement of NAS score of at least 2 points
    - percentage of patients with at least a 1 point improvement in SAF activity score
    - mean changes in NAS score, fibrosis, steatosis, hepatic ballooning, lobular inflammation, portal inflammation, SAF score, and activity score
    - changes in area of fibrosis by morphometry
    - mean changes in fibrosis using NAFLD CRN and NAFLD Ishak scoring.
- To assess the following endpoints in elafibranor treated patients relative to placebo, at Week 72, and at the end of the Long-term Treatment Period:
    - cardiovascular events
    - liver-related death events
    - changes in liver enzymes and liver markers
    - changes in noninvasive markers of fibrosis and steatosis
    - changes in lipid parameters
    - variation in body weight
    - changes in insulin resistance and glucose homeostasis markers
    - changes in inflammatory markers
    - changes in cardiovascular risk profile as assessed by Framingham scores
    - changes in quality of life (SF-36 questionnaire).
- To assess Time to first occurrence of:
    - liver cirrhosis
    - death of any cause
    - any portal hypertension or cirrhosis related events.

Study Duration (planned): estimated 72 months (First Patient First Visit [FPFV]-Last patient last visit [LPLV])

- Regulatory/ethics committee submission: January 2016
- Initiation visits: February 2016 – March 2017
- Recruitment period: February 2016 – December 2017
- FPFV: February 2016
- Interim analysis : August – October 2018
- LPLV (Long-term treatment period): December 2021

Data Safety Monitoring Board (DSMB)

An independent DSMB will be established in order to review the progress of the study and to perform a safety data review on a regular basis during the trial to protect patient welfare and preserve study integrity. The DSMB will consist of at least 4 experienced physicians (1 each of endocrinologist, cardiologist, hepatologist, and nephrologist) and 1 statistician, all of whom will be independent of the participants in the study. A DSMB Charter will define the role, responsibilities, rules and tasks of the DSMB.

Clinical events committee (CEC)

The CEC will specifically assess and adjudicate all disease progression events included in the primary composite efficacy endpoint (except for histological cirrhosis), all drug-induced liver injury events, and all major cardiovascular events: i.e. cardiovascular death, nonfatal myocardial, infarction and stroke events as defined in the CEC manual. The CEC assessment and adjudication will occur in a blinded, consistent, and unbiased manner throughout the course of a study to determine whether the endpoints meet the protocol-specified criteria.

The CEC will comprise 2 hepatologists, and 1 cardiologist, all of whom will be independent of the participants in the study.

Table 1: STUDY GENERAL ASSESSMENT SCHEDULE

	Screening Period			First Treatment Period							Long-term Treatment Period		End Of Study Treatment
Visit	**SV1**	**SV2** [4]	**SPV** [5]	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**Phone Visit PV1-PVn**	**V8-Vn**	**EOT** [13]
Week	*-12 to -8*	*-12 to -4*	*-1* [5]	*0* [6]	*12* [6]	*24* [6]	*36* [6]	*48* [6]	*60* [6]	*72* [6]	*(every 24 weeks starting 12 weeks after V7)* [8]	*(every 24 weeks starting after V7)* [9]	*30 days after final study drug administration*
Permitted Margin				0	±1 week after V1	± 1 week after V1	± 1 week after V1	± 1 week after V1	± 1 week after V1	± 1 week after V1	± 2 weeks Compared to V7	± 2 weeks Compared to V7	± 1 week after last administration
Obtain informed consent	X												
Medical history / demographics	X												
Check inclusion / exclusion criteria	X			X [7]									
Adequate diet and lifestyle recommendations, including alcohol restrictions and smoking habits	X – →												
Confirmation of diet and lifestyle compliance, including alcohol restrictions and smoking habits				X	X	X	X	X	X	X	X	X	
Physical examination	X			X	X	X	X	X	X	X		X	X
Vital signs & height [1] & weight measurement	X			X	X	X	X	X	X	X		X	X
Waist circumference	X			X		X		X		X		X	X

	Screening Period			First Treatment Period							Long-term Treatment Period		End Of Study Treatment
Visit	**SV1**	**SV2** [4]	**SPV** [5]	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**Phone Visit PV1-PVn**	**V8-Vn**	**EOT** [13]
Week	*-12 to -8*	*-12 to -4*	*-1* [5]	*0* [6]	*12* [6]	*24* [6]	*36* [6]	*48* [6]	*60* [6]	*72* [6]	*(every 24 weeks starting 12 weeks after V7)* [8]	*(every 24 weeks starting after V7)* [9]	*30 days after final study drug administration*
Permitted Margin				0	±1 week after V1	± 1 week after V1	± 1 week after V1	± 1 week after V1	± 1 week after V1	± 1 week after V1	± 2 weeks Compared to V7	± 2 weeks Compared to V7	± 1 week after last administration
12-Lead ECG				X			X			X		X [10]	X
Lab evaluation (see Table 2)	X	X		X	X	X	X	X	X	X		X	X
PK blood sampling [2]										X			
Send sample for central histological evaluation of NASH diagnosis / change	X									X		X [11]	
Liver biopsy		X [4]								X		X [11]	
Phone call to patient to confirm eligibility of histology criteria			X [5]										
FibroScan				X						X		X	
Contact the patient prior to visit [3]				X	X	X	X	X	X	X		X	X
Randomization				X									
IXRS registration	X			X	X	X	X	X	X	X	X	X	X
Review prior / concomitant medication	X			X	X	X	X	X	X	X	X	X	X

	Screening Period			First Treatment Period							Long-term Treatment Period		End Of Study Treatment
Visit	**SV1**	**SV2** [4]	**SPV** [5]	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**Phone Visit PV1-PVn**	**V8-Vn**	**EOT** [13]
Week	*-12 to -8*	*-12 to -4*	*-1* [5]	*0* [6]	*12* [6]	*24* [6]	*36* [6]	*48* [6]	*60* [6]	*72* [6]	*(every 24 weeks starting 12 weeks after V7)* [8]	*(every 24 weeks starting after V7)* [9]	*30 days after final study drug administration*
Permitted Margin				0	±1 week after V1	± 1 week after V1	± 1 week after V1	± 1 week after V1	± 1 week after V1	± 1 week after V1	± 2 weeks Compared to V7	± 2 weeks Compared to V7	± 1 week after last administration
Quality of life assessment				X		X		X		X		X [12]	X
Adverse events	X	X		X	X	X	X	X	X	X	X	X	X
Data collection on clinical outcomes					X	X	X	X	X	X	X	X	X
Study placebo or drug dispensation				X	X	X	X	X	X	X		X	
Drug accountability					X	X	X	X	X	X	X	X	X

Abbreviations: ECG = electrocardiogram; EOT = end of treatment; IXRS = Interactive voice/web Response System; NASH = nonalcoholic steatohepatitis; PK = pharmacokinetic; PV = phone visit; QOL = quality of life; SV = Screening visit; V = visit

1. Height is measured only at visit SV1.
2. At V7 (72 week treatment) a PK sampling at 2 sampling timepoints should be performed (2 hours and 5 hours 45 minutes post dosing).
3. During the study, the patient should be contacted at least 1 week before the next visit as a reminder on procedures and IP return.
4. This visit only occurs if no historical biopsy within 6 months before the Randomization Visit is available. A screening liver biopsy and slides shipment to the central anatomopathologist must be performed at least 4 weeks before Randomization (in order to obtain the results in time). Coagulation (platelet count and PT [INR]) should be checked locally prior to this liver biopsy (according to local medical standards in each hospital).
5. Screening Phone Visit. Telephone contact for all patients at least 1 week before V1. Patients should be contacted regarding eligibility confirmation within 1 week prior to Randomization Visit V1. In case of ineligibility, the patient should be contacted as soon as possible.
6. The maximum time period between visits in the First Treatment Period is to be 96 days due to the study drug supply provided to the patient.
7. Check of all inclusion/exclusion criteria, including biological and histological criteria assessed at SV1 and SV2.

8. Phone visits every 24 weeks starting 12 weeks after V7 for safety, data collection on clinical outcomes, and IP compliance control. If any information during this phone contact requires a visit, the Investigator may decide to perform an unscheduled visit. Phone visits may also be performed at the same frequency for the follow-up of patients having permanently discontinued study drug but remaining in the study (Same information collected except IP compliance control).

9. The maximum time period between visits in the Long-term Treatment Period is to be 192 days due to the study drug supply provided to the patient.

10. ECG will be performed every 48 weeks starting at V9.

11. Liver biopsy will be performed after approximately 4 years of treatment (V13) and in the case of suspicion of cirrhosis (based on FibroScan and/or clinical or biological assessment). In the case that the suspicion of cirrhosis is not confirmed by liver biopsy the patient shall remain on the study and a liver biopsy will be performed after approximately 4 years of treatment (V13, unless a biopsy has already been performed within the year). Blood sampling (coagulation tests; see Table 2) are to be performed locally before the biopsy.

12. QOL assessment questionnaire to be completed at 24 (V8), 48 (V9), and 96 (V11) weeks in the Long-term Treatment Period (following approximately 96, 120, and 168 weeks of treatment, respectively), and 48 weekly thereafter.

13. EOT Visit to be performed 30 days after final study drug administration at the end of study or for any premature discontinuation (permanent study drug discontinuation or trial discontinuation).

Table 2: STUDY BIOLOGICAL ASSESSMENT SCHEDULE

Visit	Screening Period		First Treatment Period							Long-term Treatment Period	End of Study Treatment
	SV1 SB1 [6]	SB2 [7]	V1 B1	V2 B2	V3 B3	V4 B4	V5 B5	V6 B6	V7 B7	V8 to Vn B8 to Bn	EOT
Week	*-12 to -8*	*Prior to -4*	*0*	*12*	*24*	*36*	*48*	*60*	*72*	*Every 24 weeks*	*30 days after final study drug administration*
Hematology *Hemoglobin, hematocrit, RBC, WBC, differential count, platelet count, reticulocytes count, and PT (INR)*	X		X	X	X	X	X	X	X	X	X
Coagulation - local lab testing prior to liver biopsy *Platelet count, PT (INR)* [1]		X							X	X [1]	
Serology *HIV ab I/II, HBsAg, and HCV Ab (positive HCV RNA in case HCV Ab >0* [3] *)*	X										
Screening Visit 1 - chemistry panel *HbA1c* [3]*, fasting plasma glucose, insulin (fasting), HOMA-IR creatinine, eGFR* [3]*, GGT, AST, ALT, CPK* [3]*, alkaline phosphatase, and TG*	X										
V1 to Vn total chemistry panel *HbA1c, fasting plasma glucose, creatinine, eGFR, GGT, AST, ALT, CPK, alkaline phosphatase, total proteins, albumin, electrolytes (sodium, potassium, chloride, calcium), uric acid, urea (BUN), total and conjugated bilirubin, hsCRP, total cholesterol, nonHDL-C, HDL-C, TG, calculated VLDL-C, ApoAI, ApoB, and calculated LDL-C*			X [6]	X	X	X	X	X	X	X	X
Urinalysis *albumin, creatinine, ACR, and microscopic analysis α1 microglobulin*, β-NAG,* N-Gal*, IL-18*, KIM-1*,*			X	X	X	X	X	X	X	X	X

Visit	Screening Period		First Treatment Period							Long-term Treatment Period	End of Study Treatment
	SV1 SB1 [6]	SB2 [7]	V1 B1	V2 B2	V3 B3	V4 B4	V5 B5	V6 B6	V7 B7	V8 to Vn B8 to Bn	EOT
Week	*-12 to -8*	*Prior to -4*	*0*	*12*	*24*	*36*	*48*	*60*	*72*	*Every 24 weeks*	*30 days after final study drug administration*
Urinalysis (dipstick) *Specific gravity, pH, protein, glucose, ketones, bilirubin, urobilinogen, blood, nitrite, and leukocytes*	X		X	X	X	X	X	X	X	X	X
Urinary pregnancy tests [3]	X		X	X	X	X	X	X	X	X	X
Inflammatory markers *Fibrinogen, and haptoglobin*			X		X		X		X	X	X
Other Liver markers *CK18 (M65 & M30), adiponectin, ferritin, FGF19 & FGF21, alpha2 macroglobulin, hyaluronic acid, PIIINP, TIMP-1, and CHI3L1* [4]			* [4]		*		*		* [4]	* [4]	*
Calculated fibrosis & steatosis index *Fibrotest, ELF, NAFLD Fibrosis score, Steatotest, FLI, Fibrometre S, and FIB-4*			*		*		*		*	*	*
Other safety markers *Homocysteine, NT-ProBNP, troponin-T, and cystatin C*			*		*		*		*	*	*
Special glycemic and other lipid parameters *Insulin (fasting), HOMA-IR, fructosamine, C-peptide, FFA, small dense LDL, ApoAII, Apo CIII, and Apo E*			*		*		*		*	*	*
Sampling for additional parameters *Whole blood* [5]*, plasma, and serum bank*	* [5]		*	*	*	*	*	*	*	*	*

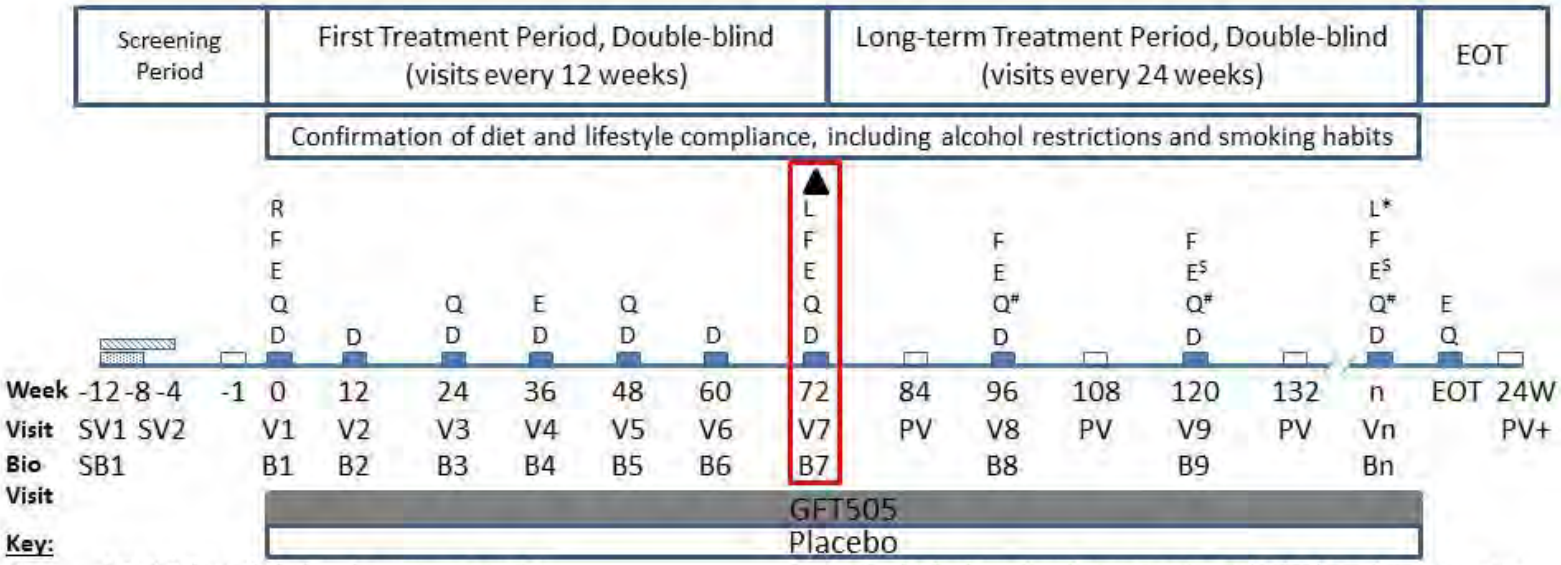
X = results available within 2 working days (routine analysis) * = batch analysis

Abbreviations Ab = antibody; ACR = albumin–creatinine ratio; Ag = antigen; ALT = alanine aminotransferase; Apo = apolipoprotein; AST = aspartate aminotransferase; β-NAG = N-acetyl-β-D-glucosaminidase; BUN = blood urea nitrogen; Bx = biological assessment Visit x; CHI3L1 = chitinase-3-like protein 1; CK18 = cytokeratin 18; CPK = creatine phosphokinase; eGFR = estimated glomerular filtration rate; ELF = enhanced liver fibrosis; EOT = end of study treatment; FFA = free fatty acid; FGF = fibroblast growth factor; FIB-4 = fibrosis 4 score; FLI

= fatty liver index; GGT = gamma-glutamyl transferase; HbA1c = hemoglobin A1c; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HDL-C = high density lipoprotein-C; HIV = human immunodeficiency virus; HOMA-IR = homeostasis model assessment of insulin resistance; hsCRP = high-sensitivity C-reactive protein; IL-18 = interleukin 18; INR = international normalized ratio; KIM-1 = kidney injury molecule-1; LDL-c = low density lipoprotein-C; NAFLD = nonalcoholic fatty liver disease; N-Gal = neutrophil gelatinase-associated lipocalin; NT-ProBNP = N-terminal of the prohormone brain natriuretic peptide; PIIINP = type III procollagen peptide; PNPLA3 = patatin-like phospholipase domain-containing protein 3; PT = prothrombin time; TIMP-1 = tissue inhibitors of metalloproteinases 1; RBC = red blood cell; SBx = Screening biological assessment Visit x; SVx = Screening Visit x; TG = triglyceride; VLDL-C = very low density lipoprotein-C; Vx = Visit; WBC = white blood cell.

1. Coagulation (platelet count and PT [INR]) should be checked prior to any liver biopsy (according to local medical standards in each hospital). To be done through a local laboratory. Liver biopsy will be performed after 72 weeks (V7) and after approximately 4 years of treatment (V13) and in the case of suspicion of cirrhosis (based on FibroScan and/or clinical or biological assessment). In the case that the suspicion of cirrhosis is not confirmed by liver biopsy the patient shall remain on the study and a liver biopsy will be performed after approximately 4 years of treatment ([V13] unless a biopsy has already been performed within the year).
2. Upon receipt of the results of the biological assessment performed at SV1, retesting or additional testing may be needed during the Screening Period:
    - CPK can be repeated prior to Randomization (V1) within 1 to 2 weeks after initial test.
    - The eGFR measurement can be repeated prior to Randomization (V1) within the following timeframe: minimum 4 weeks after initial test and maximum 2 weeks prior to planned Randomization.
    - HbA1c can be repeated prior to Randomization (V1), at the latest 2 weeks prior to planned Randomization.
    - HCV RNA, in case of positive HCV Ab, at the latest 2 weeks prior to the planned Randomization (V1).
3. Dipstick at site for WOCBP only.
4. CHI3L1 to be tested only at V1, V7, and at the time of 4 years biopsy (V13).
5. Whole blood sample will be only taken at SV1 for the analysis of PNPLA3 following DNA extraction. Plasma and serum samples should be retrieved at every visit **ONLY** for patients who have signed the genetic and biomarker ICF.
6. For DILI adjudication, to ensure adequate baseline value of the liver parameters (AST, ALT, total bilirubin, INR), at least 2 consecutive assessments at least 8 weeks apart between Visit SV1 and Visit V1 should be performed. SV1 and Visit V1 should be scheduled according to this requirement.
7. SB2, additional visit in the Screening Period if required for coagulation prior to liver biopsy.

Figure 1: STUDY DURATION AND VISIT SCHEDULE



Key:

Bio Visit	Scheduled visits for biological assessment sampling	D	Study placebo or drug dispensation. No study placebo or drug dispensation will occur on the final Vn visit during the Long-term Treatment Period.
E	Electrocardiogram (ECG)	EOS	End of study
EOT	End of study treatment visit performed 30 days after final study drug administration at the end of study or for any premature discontinuation (permanent study drug discontinuation or trial discontinuation)	PV PV+	PV for safety, data collection of clinical outcomes and IP compliance control After EOT, patients without study outcome, can be followed up by 24weekly phone visits for safety and clinical outcomes up to the EOS.
L	Liver biopsy	F	FibroScan
Q	Quality of Life questionnaire	R	Randomization
S	Screening		Visit including clinical and laboratory evaluations
	Potential SV2 and SB2 visits for liver biopsy (if no historical biopsy 6 months prior to visit 1)		Phone visit (for confirmation of eligibility in Week -1, for safety and drug accountability in Long-term Treatment Period, and for safety, diagnosis of cirrhosis and occurrence of clinical outcomes including liver and cardiovascular events for patients who have discontinued study drug for reasons other than an event in the primary composite endpoint for long-term efficacy [24 weekly after EOT])
	Screening visits SV1 and SB1 to occur between Weeks -12 and -8	$	ECG performed 48 weekly starting at visit V9
#	Quality of life questionnaire in Long-term Treatment Period performed at Visits V8, V9, and V11, and 48 weekly thereafter	*	Liver biopsy performed at approximately 4 years (visit V13) and in the case of suspicion of cirrhosis
	Interim analysis performed and filed for initial market approval under Subpart H	▲	PK sampling

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AASLD	American Association for the Study of Liver Diseases
ACR	albumin–creatinine ratio
ADR	adverse drug reaction
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	Analysis of Covariance
ApoAI	apolipoprotein AI
ApoAII	apolipoprotein AII
ApoB	apolipoprotein B
ApoCIII	apolipoprotein CIII
AST	aspartate aminotransferase
AT	aminotransferase
ATP	Adult Treatment Panel
BMI	body mass index
BP	blood pressure
BUN	blood urea nitrogen
Bx	biological assessment visit
CA	competent authorities
CEC	Clinical Events Committee
CFR	Code of Federal Regulations
CPK	creatine phosphokinase
CRN	Clinical Research Network
CRO	Clinical Research Organization
CRP	C-reactive protein
CSR	Clinical Study Report
CYP	cytochrome P450
DDI	drug-drug interaction
DILI	drug-induced liver injury
DSMB	Data Safety Monitoring Board
EASL	European Association for the Study of the Liver
ECG	electrocardiogram
eCRF	electronic case report form
EES	efficacy evaluable sample
eGFR	estimated glomerular filtration rate
EOS	end of study
EOT	end of study treatment
FDA	Food and Drug Administration
FFA	free fatty acid
FIB-4	fibrosis 4 score
FLI	fatty liver index
FPFV	first patient first visit
FSS	Full safety set
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GLP1	glucagon-like peptide 1

HbA1c	hemoglobin A1c
HBsAg	hepatitis B surface antigen
HCC	hepatocellular carcinoma
HCV	hepatitis C Virus
HDL-C	High-density lipoprotein cholesterol
HIV	human immunodeficiency virus
HOMA-IR	homeostasis model assessment of insulin resistance
hPPAR	human peroxisome proliferator-activated receptor
HRT	Hormonal replacement therapy
HSC	hepatic stellate cells
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
INR	international normalized ratio
IP	investigational product
IR	insulin resistance
IRB	Institutional Review Board
ITT	intent-to-treat
IXRS	Interactive Voice/Web Response System
LDL-C	Low-density lipoprotein cholesterol
LPLV	last patient last visit
[redacted]	[redacted]
M2	anti-inflammatory macrophages
MedDRA	Medical Dictionary for Regulatory Activities
MELD	model end stage liver disease
NAFLD	nonalcoholic fatty liver disease
NAS	NAFLD Activity Score
NASH	nonalcoholic steatohepatitis
NCEP ATP III	National Cholesterol Education Program's Adult Treatment Panel III
PD	pharmacodynamics
PK	pharmacokinetics
PPAR	peroxisome proliferator-activated receptor
PPS	per protocol set
PT	prothrombin time
PUFA	polyunsaturated fatty acids
QD	once daily
QTc	corrected QT
SADR	serious adverse drug reaction
SAE	serious adverse event
SAF	steatosis, activity, and fibrosis
SAP	Statistical Analysis Plan
SBx	screening biological assessment visit
SF-36	36-Item Short-Form Health Survey
SGLT2	sodium/glucose cotransporter 2
SOP	Standard Operating Procedure
SS	safety set
SUSAR	suspected unexpected serious adverse reactions

SVx	Screening Visit x
TLC	therapeutic lifestyle change
TNFα	Tumor Necrosis Factor-alpha
ULN	upper limit of normal
UV-LLNA	UV- Local Lymph Node Assay
Vx	Visit x
WOCBP	women of childbearing potential

1. INTRODUCTION

1.1. NONALCOHOLIC STEATOHEPATITIS

Nonalcoholic fatty liver disease (NAFLD) is a spectrum of disorders characterized by excessive fat accumulation in the liver (steatosis). Nonalcoholic steatohepatitis (NASH) defines a subgroup of NAFLD where steatosis coexists with hepatocyte injury and inflammation (steatohepatitis), with or without fibrosis.

Nonalcoholic steatohepatitis is considered by the European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Diseases (AASLD) as an increasing public health issue owing to its close epidemiological association with the worldwide epidemic of obesity and type 2 diabetes.

The prevalence of NAFLD in the general population assessed by ultrasonography is 20% to 30% in Europe. A similar prevalence of 15% to 25% was documented histologically by postmortem studies. A high prevalence of histological NAFLD has been described in apparently healthy liver donors: 12% to 18% in Europe and 27% to 38% in the US. Furthermore, with a sensitive technique such as magnetic resonance spectroscopy, 34% have NAFLD.

Interestingly, 39% of newly diagnosed cases of chronic liver disease had NAFLD, making NASH one of the top causes of liver diseases in Western countries. Using the histological definition of NASH, recent studies have shown a high prevalence of NASH among NAFLD cases: 43% to 55% in patients with increased aminotransferases, 49% in morbidly obese patients, and 67% in a subset of patients with incident chronic liver disease. Finally, in apparently healthy liver donors the prevalence of NASH ranges from 3% to 16% in Europe and from 6% to 15% in the US.

The commonest cause of NASH is primary NAFLD-associated insulin resistance and its phenotypic manifestations, namely excess weight/obesity, visceral obesity, type 2 diabetes, hypertriglyceridemia, and arterial hypertension. A causal association has been suggested by longitudinal studies showing a chronological association between the progression of insulin resistance, the metabolic syndrome and the occurrence of NAFLD/NASH.

1.2. PATHOPHYSIOLOGICAL PROCESS OF NONALCOHOLIC STEATOHEPATITIS

A widely described model suggests that the development of NAFLD into NASH requires several 'hits' or insults.[1,2] According to this model, increased hepatic levels of free fatty acid (FFA) consequent to impaired insulin sensitivity in the liver and peripheral tissues may serve as the first hit. The increased hepatocyte FFA load would further increase insulin resistance (IR), steatosis, oxidative stress with lipid peroxidation, endoplasmic reticulum stress, resulting in inflammatory cell accumulation and activation into the liver (second hit). This finally leads to hepatocyte growth arrest or apoptosis, which activates hepatic progenitor cells and associated bile ductular proliferations, cells that initiate inadequate repair by producing a diverse range and high concentrations of profibrogenic cytokines and growth factors that activate hepatic stellate

cells (HSC) and perivascular or portal fibroblasts. The activated HSC themselves can release chemotactic factors that recruit inflammatory cells, creating a deleterious feedback inflammatory loop' that leads to fibrogenesis. Collagen and other extracellular matrix components accumulate within the liver, which may result in distortion of the hepatic architecture and finally cirrhosis. Thus, in this "multiple-hit" model IR can be considered as the first step on the pathogenic road leading to NASH, fibrosis and cirrhosis.

However, this "multiple-hit" model has been recently challenged by data suggesting that mechanisms that can drive disease progression can also induce steatosis. Oxidative stress and gut flora/cytokines can induce steatosis as well as necroinflammation and fibrosis. Free fatty acids can initiate hepatocyte apoptosis in addition to being esterified to triglycerides. Endoplasmic stress can also lead to steatosis, oxidative stress, and apoptosis. Since all these mechanisms are important in obesity and IR, it would seem likely that they are the true "first hits" leading to increased hepatic FFA flux and oxidative-, endoplasmic reticulum-, and cytokine-mediated stress that result in both steatosis and progressive liver damage. Steatosis should therefore be considered part of the liver's early "adaptive" response to stress, rather than a first hit in disease progression. Accordingly, while in some situations its severity may act as a biomarker of ongoing injurious and fibrotic mechanisms resulting in disease progression, it should not be considered a sole therapeutic target. Instead attention should be paid on the mechanisms of cellular injury and fibrosis – the "second hits."

Oxidized by-products are harmful adducts that can cause liver injury, resulting in subsequent fibrosis.[3] Lipid peroxidation and oxidative stress up-regulate liver fibrosis via activation of stellate cells and increased production of Transforming Growth Factor-beta.[4] Over expression of uncoupling proteins has been associated with a reduction in generation of reactive oxygen species and Kupffer cell activation, which might attenuate injury in NAFLD. In addition to insulin resistance, several authors have shown that leptin contributes to an insulin-resistant state and might even stimulate fibrogenesis in animal models of NAFLD.[5]

Inflammatory mediators have been implicated in the progression of NAFLD and are the focus for new therapeutics. Pro-inflammatory transcription factors such as Nuclear Factor kappa B (NF-κB) are often elevated in patients with NASH.[6] Tumor Necrosis Factor-alpha (TNFα) is another inflammatory mediator largely produced by macrophages, but also by other cells including adipocytes and hepatocytes. Elevated levels of TNFα have been detected in obese patients with insulin resistance and NASH. The TNFα-mediated hepatic injury results from the inhibition of mitochondrial electron transport and release of reactive oxygen species that stimulate lipid peroxidation. On another hand, adiponectin decreases fatty acid oxidation and inhibits hepatic gluconeogenesis.[7] Both human and mouse models have demonstrated that lower adiponectin levels are associated with increased severity of hepatic inflammation.[8,9] The TNFα is an inflammatory mediator largely produced by macrophages, but also elaborated by other cells including adipocytes and hepatocytes.[1,10] Elevated levels of TNFα have been detected in obese patients with insulin resistance and NASH.[11,12] TNFα-mediated hepatic injury results from inhibition of mitochondrial electron transport and release of reactive oxygen species that stimulate lipid peroxidation.[10]

Recently, scientists have focused on the role of Kupffer cells in the pathogenesis of NAFLD. Kupffer cells are the resident macrophages of the liver and function in both innate and adaptive immunity as active phagocytosing agents and antigen-presenting cells (via toll-like receptors) to T-cells. Finally, the proapoptotic gene Bax is upregulated in patients with NASH and alcoholic liver disease.[13] Additionally, caspase levels, by-products of cellular apoptosis, are also increased in these groups of patients.

1.3. ELAFIBRANOR: RATIONALE FOR A MIXED PPAR ALPHA/DELTA AGONIST IN NASH

The GENFIT drug candidate, elafibranor, and its main active circulating metabolite, GFT1007, are dual peroxisome proliferator-activated receptor (PPAR)α/δ modulators with preferential activity on PPARα over PPARδ (about fivefold more potent on human PPAR [hPPAR]α than on hPPARδ). The PPARδ properties of elafibranor and GFT1007 have been demonstrated in both human skeletal muscle cells (a pure PPARδ response) and human hepatocytes (a mixed PPARα/δ response).

The PPARα receptors are most prominently expressed in the liver and can be activated by drugs of the fibrate class. Activation results in increased uptake and oxidation of FFAs, increased triglyceride hydrolysis and upregluation of apolipoprotein (Apo)A-I and ApoA-II. The net effect is fatty acid oxidation, decrease in serum triglycerides, a rise in high-density lipoprotein cholesterol (HDL-C) levels, and an increase in cholesterol efflux. The PPARα activation has also anti-inflammatory effects via inhibition of COX2, IL-6, and C-reactive protein (CRP). Some PPARα compounds have proved their effectiveness in animal models like Methionine-Choline-Deficient diet model or CCl4 in reducing the steatosis. However, clinical trials with fibrates in human NASH have been unimpressive. For example in a pilot study, 12 months treatment with clofibrate in 16 patients with NASH and elevated triglycerides had no impact on liver enzyme elevation or triglycerides levels.[14]

The PPARδ appears to be a powerful metabolic regulator, with actions on fat, skeletal muscle, liver, and heart. Its activation enhances fatty acid transport and oxidation, improves glucose homeostasis via improved insulin sensitivity and inhibition of hepatic glucose output, turns off macrophage inflammatory responses, and dramatically increases circulating HDL-C levels. Thus selective PPARδ agonists have the potential to target multiple components of the metabolic syndrome, including obesity, dyslipidemia, hypertriglyceridemia insulin resistance, and probably NASH.

Accordingly, PPARδ ligands also show promise in chronic inflammatory models of hepatotoxicity.[15] Notably, biomarkers of liver toxicity, including serum alanine aminotransferase (ALT), hepatic TNFα, TNF-like weak inducer of apoptosis receptor, were all higher in carbon tetrachloride-treated PPARδ knockout mice compared to wild-type mice. GW0742 reduced serum ALT, TNFα, S100A6, MCP1, and TNF-like weak inducer of apoptosis receptor in wild-type mice, but not PPARδ knockouts.

Finally, in a short clinical trial, a pure PPARδ agonist, GW501516, has demonstrated efficacy on liver fat content while improving insulin resistance and decreasing γGT.[16]

Considering the emerging role of Kupffer cells in the pathogenesis, 2 recent publications identified PPARδ as a crucial signaling receptor controlling the phenotypic switch between classical pro-inflammatory and alternative anti-inflammatory (M2) macrophages.[17,18] These studies demonstrate that PPARδ encourages macrophages toward the alternative M2 phenotype, which improves fatty acid metabolism, insulin sensitivity, and suppresses inflammation. The finding raise the possibility that small molecule agonist of PPARδ may be effective therapeutic targets for the treatment of chronic inflammation in the liver.

The match between the activation of PPARα and PPARδ in the liver may thus improve NASH. Accordingly, in several well-established experimental models of NAFLD/NASH and liver fibrosis, treatment with elafibranor confers liver protection both in preventive and therapeutic approaches on established pathologies. These effects have been demonstrated through plasma and hepatic markers, as well as liver macro- and micro- histological examination. These studies have shown that elafibranor acts on several mechanisms involved in NASH pathogenesis: steatosis, inflammation, and fibrosis pathways. Complementary studies have demonstrated that both PPARα-dependent and PPARα-independent mechanisms participate in the beneficial effects of elafibranor on NAFLD/NASH.

1.4. SUMMARY OF NONCLINICAL STUDIES

1.4.1. Pharmacology

In several well-recognized experimental models of NAFLD/NASH, treatment with elafibranor confers liver protection both in preventive and therapeutic approaches on established pathologies. These effects have been demonstrated through plasma and hepatic markers, as well as liver macro- and micro-histological examination. These studies have shown that elafibranor acts on several mechanisms involved in NASH pathogenesis: steatosis, inflammation, and fibrosis pathways. Complementary studies have demonstrated that both PPAR-dependent and PPAR-independent mechanisms participate in the beneficial effects of elafibranor on experimental NAFLD/NASH.

Besides hepatoprotection, the efficacy of elafibranor has been assessed in numerous pharmacological preclinical models of metabolic disorders.

Briefly, in experimental models of type 2 diabetes, elafibranor has insulin-sensitizing and glucose lowering properties. In db/db mice, a 28-day treatment with elafibranor produced a dose-dependent decrease in fasting plasma glucose and glycated hemoglobin (HbA1c), comparable to the effect of rosiglitazone. However, in contrast to the PPARγ reference agonist, elafibranor did not increase plasma adiponectin, thus ruling out a PPARγ -mediated effect on adipose tissues. Similarly, in ob/ob mice, elafibranor ameliorated plasma glucose and insulin levels without modulating plasma adiponectin or inducing PPAR target genes in adipose tissues.

Besides its effects on NAFLD/NASH and type 2 diabetes, oral treatment with elafibranor in a mouse model of dyslipidemia potently reduced plasma triglycerides and total cholesterol through the induction of PPARα

target genes in the liver and by reduction of ApoCIII gene expression. In parallel, elafibranor increased plasma HDL-C levels more potently than the PPARα reference compound fenofibrate. The chronic treatment of these mice fed a high fat diet with elafibranor prevented the development of atherosclerotic plaques in the aorta.

1.4.2. Safety pharmacology

Any potential effect on the cardiovascular, respiratory, and central nervous system has been assessed and no safety issue was identified.

1.4.3. Absorption/distribution/metabolism/excretion studies (ADME)

In animal studies, elafibranor was well and rapidly absorbed although absolute bioavailability was moderate (about 20% to 40%). Elafibranor is extensively metabolized and the activity is mainly carried by the active metabolite GFT1007. In rat and dog, maximal plasma concentrations and exposure for both elafibranor and GFT1007 linearly increase with the dose after single or repeated administrations. Elafibranor and its metabolites are rapidly cleared from the plasma and they are totally excreted by both fecal and renal route within 48 hours. In the rat elafibranor and/or its metabolites are rapidly excreted into the bile and undergo an extensive entero-hepatic cycle giving support for liver targeting of elafibranor and/or GFT1007. The distribution study in the rat supports the liver targeting of elafibranor and/or its metabolites.

In vitro elafibranor does not inhibit cytochrome p450 (CYP)1A2, CYP3A4, and CYP2D6 with moderate inhibition of CYP2C9 and weak inhibition of CYP2C8, CYP2C19, and CYP4A11. GFT1007 does not produce any inhibition of the CYP450 isoforms 1A2, 3A4, 2C19, and 2D6, and only weak inhibition of CYP2C8 and CYP2C9. Both molecules also show weak inhibition of CYP3A4/5, but only with midazolam as substrate. Thus, the risk of drug-drug interaction due to an inhibition of the main cytochromes involved in drug metabolism should be limited. Potential interaction with CYP2C9 metabolized drugs has been assessed through a clinical study (GFT505-112-8) designed to evaluate potential pharmacokinetic (PK) interaction of elafibranor 120 mg administered for 14 days alone or with a single administration of warfarin. This study demonstrated that elafibranor administration did not affect the PK profile of warfarin (R-warfarin and S-warfarin).

A protein binding study showed that elafibranor and GFT1007 were highly bound to human serum albumin. The risk of drug-drug interaction due to albumin binding should be limited since this binding is not saturable.

In vitro studies have been performed to determine whether elafibranor (GFT505) and it principal metabolite GFT1007 are substrates and/or inhibitors of major drug transporters, in order to assess the potential for drug-drug interaction (DDI). Based on the results of the OATP1B3 transporter inhibition assay,

elafibranor (GFT505), has recently been assessed in a follow-up clinical DDI study with the OATP1B3-sensitive substrate, atorvastatin.

For the other drug transporters studied, the interaction observed does not require follow-up studies based on current regulatory guidance.

The metabolic stability and metabolism pathways of elafibranor (GFT505) have been studied on liver microsomes and in primary hepatocytes from rat, dog, mouse, monkey, and human. There was no evidence of the formation of unique human metabolites or metabolites formed at disproportionately higher levels in human hepatocytes than in any other species.

An in vivo study has been performed to compare the bioavailability of ^{14}C-GFT505 in the rat, dog, minipig and monkey. This study showed that in all species ^{14}C-GFT505 is rapidly absorbed, although absolute bioavailability was moderate (about 20% to 40%).

1.4.4. Toxicology

1.4.4.1. Mutagenicity and genotoxicity

The toxicology program performed according to International Council for Harmonisation (ICH) guidelines demonstrates that elafibranor has no genotoxic or mutagenicity potential.

1.4.4.2. Acute toxicity

According to acute toxicity studies results, it can be concluded that elafibranor is extremely safe when administered as single oral doses in rat and mouse, since no sign of toxicity was detected up to the dose of 1000 mg/kg.

1.4.4.3. Repeated dose toxicity studies

The safety of elafibranor has been assessed in multiple preclinical toxicology studies with repeated-dose oral administration for up to 6 months in rats and 12 months in monkeys. Moreover, two-year repeated-dose carcinogenicity studies in mice and rats have been completed.

The only consistent safety concern raised by these studies is the expected PPARα-associated hepatomegaly, hepatocellular hypertrophy, and liver carcinoma in rodent species (mice and rats). However, it is well known that, compared to nonhuman primates and humans, rodents are highly sensitive to PPARα agonist induced peroxisome proliferation and associated liver side effects. Thus, available information on this class of drug which includes marketed fibrates together with the lack of any liver side effects in monkeys treated with high doses of elafibranor for 1 year support the nonrelevance to human.[19] Overall, these studies did not reveal any other safety issues up to the highest doses tested. Notably, elafibranor did not have any of the known PPARγ-related concerns such as excess in weight gain, hemodilution, edema, cardiomegaly, adiponectin induction, or urinary bladder carcinoma.

1.4.4.4. Photoxicity studies

The phototoxic potential of elafibranor has been assessed by the in vitro 3T3 NRU phototoxicity test and the UV- Local Lymph Node Assay (LLNA) test in mice. Elafibranor (GFT505), but not its major metabolite GFT1007, showed UVA-dependent cytotoxicity in vitro. The UV-LLNA test was performed in mice with oral dosing for 3 days at up to 800 mg/kg/day elafibranor. Although a very conservative no observed effect level (NOAEL) was set at 400 mg/kg/day based on isolated findings at the highest dose, it is considered that data are more in favor of an absence of phototoxic effect, given the tissue distribution of elafibranor (GFT505), and absence of photoxicity signal in the clinical studies.

1.5. CLINICAL STUDIES

1.5.1. Phase I program

A Phase I program to assess the safety and tolerability as well as the PK profile of elafibranor has been conducted through 12 clinical trials, one of them ongoing. A total of 608 volunteers were randomized in these studies performed in Phase I centers, including 536 healthy lean subjects, 60 overweight or obese subjects, and 12 patients with type 2 diabetes.

The plasma concentrations of elafibranor and GFT1007 were determined using validated high-performance liquid chromatography tandem mass spectrometry methods. The PK parameters were calculated using a noncompartmental analysis.

In healthy volunteers, the PK of elafibranor and GFT1007 after single administration of elafibranor at rising dose levels were assessed in 2 distinct double-blind, placebo-controlled randomized trials from 10 to 120 mg (GFT505-106-1 and GFT505-108-4). The PK of elafibranor and GFT1007 after repeated doses of elafibranor at rising dose levels were assessed in 3 distinct double-blind, placebo-controlled randomized trials: GFT505-106-2 (5, 10, 20, and 30 mg/d), GFT505-108-4 (40, 60, 80, and 100 mg/d) and GFT505-113-9 (300 and 360 mg/d).

In overweight/obese but otherwise healthy volunteers, the PK of elafibranor and GFT1007 after single administration of elafibranor at rising dose levels from 180 to 300 mg were assessed in a double-blind, placebo-controlled randomized trial (GFT505-111-7). In the same trial, the PK of elafibranor and GFT1007 after repeated doses of elafibranor at dose levels from 120 to 240 mg, were assessed in overweight/obese but otherwise healthy volunteers. Another part of this trial assessed the PK of elafibranor and GFT1007 after repeated doses of elafibranor at 180 mg in type 2 diabetic patients.

The food effect on PK of elafibranor and GFT1007 was assessed in healthy volunteers at the dose of 30 mg elafibranor in a Phase I, randomized, crossover trial (GFT505-106-1).

The PK of elafibranor and GFT1007 obtained after administration of the different formulations used throughout clinical evaluation of elafibranor were compared in dedicated clinical trials in healthy

volunteers: GFT505-108-3, GFT505-111-7, and GFT505-115-12. Comparable relative bioavailability was demonstrated.

The lack of PK DDI between elafibranor (80 mg/d) and Simvastatin has been verified (GFT505-109-5).

The lack of effect of a concomitant administration of sitagliptin on elafibranor PK has been verified (GFT505-109-6).

The lack of effect of elafibranor administration (120 mg/d) on the PK and pharmacodynamics (PD) of warfarin has been verified (GFT505-112-8).

The lack of effect of elafibranor administration (180 mg/d) on the PK and PD of atorvastatin has been verified (GFT505-115-11).

The study GFT505-113-9 evaluated the effect of multiple oral doses of elafibranor on the QT/corrected QT (QTc) interval compared to placebo with moxifloxacin (400 mg in single oral dose) as a positive control, in healthy male and female volunteers. No effect of elafibranor on QT/QTc interval at both therapeutic and supratherapeutic doses for 14 days was observed.

The excretion balance of radiocarbon (i.e., the sum of ^{14}C-labeled elafibranor and its ^{14}C-labeled metabolites) and the metabolite profiling and PK of elafibranor after a single oral dose of 120 mg ^{14}C-labeled elafibranor have been assessed (GFT505-114-10). Most of the radiocarbon was excreted in feces (77.1%) and urine (19.3%), giving a recovery of 96.3% of the administered dose. The metabolite profile was assessed in plasma, urine, and feces, and did not highlight any new Phase I metabolite but allowed the identification of new glucuronated metabolites, one of them being the main urinary metabolite (12% of the administered dose).

Part of the study GFT505-115-12 is still ongoing. The objective is to assess the dose linearity after single oral administration of 120, 180 and 240 mg of elafibranor, and if confirmed, to assess the time dependency of the PK parameters after single and multiple oral administration of therapeutic dose of elafibranor.

1.5.2. Phase II program

A Phase II program was initiated to assess the safety, and efficacy profile of elafibranor in patients suffering from cardiometabolic disorders. To date, 5 Phase IIa pilot trials have been completed in which 297 patients were randomized. A Phase IIb trial has recently been completed (Clinical Study Report [CSR] not yet available), and evaluated the efficacy and safety of elafibranor 80 mg and 120 mg on steatohepatitis in 274 patients with NASH.

A Phase IIa pilot study (GFT505-207-1) was first conducted to evaluate the efficacy, safety and tolerability of elafibranor at 30 mg/d for 28 days in patients with Fredrickson type IIb dyslipidemia. Thirty-seven randomized patients received elafibranor 30 mg (24 patients) or placebo (13 patients) over a 28-day

treatment period. Although improvements were observed on primary lipid parameters, these trends were not statistically significant versus placebo.

The Phase IIa study (GFT505-208-3) assessed efficacy and safety in men and postmenopausal women with atherogenic dyslipidemia (high triglycerides, low HDL-C) and abdominal obesity treated once a day for 28 days with 80 mg/d of elafibranor. Ninety-four patients were randomized: 63 patients in the elafibranor 80 mg/d arm and 31 patients in the placebo arm.

The Phase IIa study (GFT505-209-4) assessed efficacy and safety in patients treated for 35 days with elafibranor at 80 mg/d. This study targeted patients with impaired fasting glucose and impaired glucose tolerance associated with abdominal obesity. Forty-seven patients were randomized: 23 patients in the elafibranor 80 mg/d arm and 24 patients in the placebo arm.

The Phase IIa study GFT505-210-5 assessed efficacy and safety in patients with type 2 diabetes mellitus. Patients were treated once a day for 12 weeks with 80 mg/d of elafibranor. Ninety-seven patients were randomized: 50 patients in the elafibranor 80 mg/d arm and 47 patients in the placebo arm.

The Phase IIa study (GFT505-210-6) was designed to evaluate the safety and efficacy of elafibranor on hepatic and peripheral insulin sensitivity using the gold standard glucose clamp technique in male patients with homeostasis model assessment of insulin resistance (HOMA-IR) >3 and abdominal obesity. Patients were treated once daily (QD) with 80 mg/d of elafibranor or placebo for 8 weeks in a crossover design. In this study, after 8 weeks of treatment, elafibranor significantly improved the response of the liver to insulin action. Indeed, at the first level of insulin perfusion, the insulin-induced decrease in hepatic glucose production was -49±4% after elafibranor versus -34±4% after placebo (p=0.0016). The insulin sensitivity of the muscles and other peripheral tissues measured at the second level of insulin perfusion was also increased by 28% with a significant effect on the glucose infusion rate (3.69±0.31 mg/kg/min after elafibranor versus 3.21±0.31 mg/kg/min after placebo, p=0.048). Moreover, at the end of the treatment period, elafibranor significantly lowered the FFA levels measured at the first insulin level (FFA 0.21 mEq/L after elafibranor versus 0.27 mEq/L after placebo, p=0.006).

The favorable effect of elafibranor on insulin sensitivity and glucose homeostasis was also observed in studies GFT505-209-4 and GFT505-210-5. In prediabetic patients with impaired fasting glucose, impaired glucose tolerance, and abdominal obesity (study GFT505-209-4), treatment with elafibranor 80 mg/d for 28 days led to a significant decrease in fasting plasma glucose (-5%, p=0.04), fasting plasma insulin (-25%, p=0.009), and consequently improvement of the insulin resistance index (HOMA-IR: -31%, p=0.027). In diabetic patients treated for 3 months with 80 mg/d of elafibranor (study GFT505-210-5), oral glucose tolerance test-derived parameters, including area under the time-concentration curve for glycemia, insulinemia and FFA levels, significantly improved.

In all Phase IIa studies, patients treated with elafibranor at 80 mg/d for 1 to 3 months consistently experienced an improvement of the plasma lipid profile, with significant reduction of triglycerides

(-20% to -35%), reduction in low-density-lipoprotein cholesterol (LDL-C) (-10% to -15% in prediabetic, insulin-resistant and diabetic patients) and increase in HDL-C (+10% in patients with atherogenic dyslipidemia). In addition, elafibranor treatment consistently increased the anti-atherogenic apolipoproteins (ApoAI and ApoAII) while reducing the pro-atherogenic apolipoproteins (ApoB, ApoCIII, ApoE).

In all Phase IIa studies, elafibranor treatment at 80 mg/d for 1 to 3 months also led to favorable reductions in inflammatory markers. Reduced haptoglobin levels were observed in all Phase IIa clinical trials with elafibranor, with the greatest effect obtained after 3 months of treatment in diabetic patients (-20% in the elafibranor group versus +6% in the placebo group, $p<0.001$). Similarly, fibrinogen levels were consistently decreased by approximately 10% in all Phase IIa clinical trials with elafibranor, and high-sensitivity CRP levels were lowered after 3 months of treatment in diabetic patients (-17% in the elafibranor group versus +52% in the placebo group).

Finally, beneficial effects of elafibranor on liver function were consistently observed in all Phase IIa clinical trials of patients treated for 1 to 3 months with 80 mg/d elafibranor. Significant reductions in circulating levels of gamma-glutamyl transferase (GGT) were observed in each study and reached up to -29% in elafibranor treated groups compared to placebo. In addition, in insulin-resistant patients, elafibranor treatment induced a significant reduction in ALT (-20% compared to placebo), while the level of aspartate aminotransferase (AST) was unchanged.

A Phase IIb study in NASH patients (GFT505-212-7) included 274 patients and involved a total of 56 centers in the US and in multiple European countries (France, Belgium, The Netherlands, Italy, UK, Germany, Spain, and Romania). The study evaluated the efficacy and safety of elafibranor at 80 and 120 mg QD for 52 weeks versus placebo in reversing histological steatohepatitis without worsening of fibrosis.

The study analyses showed that elafibranor at 120 mg demonstrates efficacy on the resolution of NASH without worsening of fibrosis in patients with an active disease (NAFLD Activity Score [NAS] score ≥4). Importantly, elafibranor at 120 mg concomitantly improved the cardiometabolic risk profile of NASH patients by decreasing plasma triglycerides, total and LDL-C, increasing HDL-C and improving inflammation, insulin resistance and glucose homeostasis.

The good safety profile of elafibranor was confirmed in this study. Elafibranor was well tolerated, at both doses. From the start to end of the study, regular safety reviews did not generate any comment or additional request from the Data Safety Monitoring Board (DSMB). The most frequent and expected adverse events were of gastrointestinal nature. Clinical adverse events were generally mild to moderate in severity and were similar in the placebo and treated groups for the most frequently reported treatment-related AEs. Leukocyturia, hypoglycemia and diabetes mellitus inadequate control were more frequent in elafibranor arms as well as cutaneous rash, arthralgia, decrease in appetite, dizziness and renal impairment which were only reported in the elafibranor treated groups. . Serious adverse events (SAE) were reported in 27 patients treated with elafibranor (13 with elafibranor 80 mg/d and 14 with elafibranor 120 mg/d). Of

these, only 6 SAEs reported in 4 patients treated with elafibranor were considered as related to treatment. Nineteen patients discontinued the study for safety reason with no imbalance between groups (6 in the placebo arm, 6 in the elafibranor 80 mg arm, and 7 in the elafibranor 120 mg arm).

1.6. CONCLUSION

Clinical data confirmed the beneficial effect of elafibranor in NASH patients, with efficacy on histology associated with improvement on insulin resistance, and with relevant reductions in markers of liver injury such as GGT and ALT, and in inflammatory markers. It demonstrated also improvement in lipid profile resulting in a beneficial balance between pro and anti-atherogenic markers. Moreover, it highlighted the good safety profile of elafibranor, since no major safety concerns were raised during these studies.

For additional information see Investigator's Brochure.

1.7. RATIONALE FOR STUDY POPULATION

Given the natural fluctuation of the disease for patients with mild NASH (NAS score of 3), phase IIb study results have clearly highlighted that only NASH patients with moderate to severe disease (NAS score≥4) should be treated.

Regarding fibrosis, available data from meta-analyses demonstrate that NASH patients are at greatest risk of progression to advanced fibrosis, cirrhosis and liver outcomes. Patients with NASH develop progressive fibrosis in 25% to 50% of individuals over 4-6 years, while 15% to 25% of individuals with NASH can progress to cirrhosis.[20] In another study, with a mean follow-up of 13 years, 13.3% of NASH patients with mild to moderate fibrosis (stage 1-2) and 50% of patients with fibrosis stage 3 at inclusion developed cirrhosis.[21]

Considering these data, it is reasonable to include NASH patients with any stage of fibrosis (stage 1 to 3) in the Phase III program, from both safety and prospect for benefit standpoints. However, since in patients with NASH and advanced fibrosis (F2-F3) the probability of developing cirrhosis is much higher than in patients with early fibrosis (F1), the population evaluated for the long-term outcome needs to be based on the advanced fibrosis patients in order to enhance the chances of demonstrating a benefit within a reasonable timeframe.

Accordingly, the target population for the analysis of surrogate endpoint and liver outcomes will be NASH patients with advanced fibrosis (F2-F3). The enrollment of patients with advanced fibrosis for the evaluation of long-term outcomes including progression to cirrhosis should ensure that an expected number of events, calculated based on progression rate for each fibrosis stage, are obtained. Based on the literature, [21,22,23,24,25] in patients with NASH and advanced fibrosis (F2-F3) this progression rate can be estimated at 8% per year for fibrosis stage 3 and 6% per year for fibrosis stage 2, thus an average of 7% for advanced fibrosis.

As a conservative approach, no supplementary percentage was added to the estimated progression rate to histological cirrhosis (7%) for all the other events of the composite endpoint not linked to cirrhosis. Generally, liver decompensation events occur only when cirrhosis is present and the progression rate to the other events is expected to be very low.

A limited number of NASH patients with fibrosis stage 1 and associated comorbidities known to be at risk of fast disease progression will be included in the study as an exploratory group.

Enrollment of female patients will be capped at 40% in each group for this study to mirror the higher prevalence of NASH in males compared to females.[26]

1.8. JUSTIFICATION OF THE SELECTED DOSE

The results obtained in the Phase IIb study evaluating the resolution of NASH clearly demonstrated the superiority of the elafibranor dose of 120 mg over 80 mg on the histological endpoint, regardless of the population selected (Intent-To-Treat [ITT] or Full Analysis Set) or the subgroup tested, indicating that the dose to be used for the Phase III trial should be 120 mg.

To support this assumption, a dose-response modeling was performed based on data obtained in the Phase I clinical program with 14-day repeated dose studies ranging from 5 mg to 360 mg daily dose. In this model, the studied response was the change at endpoint versus baseline in biochemical parameters known to be associated in a dose-dependent manner with elafibranor exposure, such as liver enzymes (ALT, GGT, alkaline phosphatase), plasma lipids (triglycerides, LDL-C, HDL-C) or serum creatinine. Based on this modeling, the optimum dose was consistently assessed as a value of 118 mg. Therefore, given its good safety profile and evidence of efficacy, both supported by the dose-response modeling, 120 mg elafibranor appears to be the most appropriate dose for the upcoming Phase III trial.

1.9. RATIONALE FOR EFFICACY ENDPOINT

1.9.1. Primary endpoint for application under conditional approval

Steatohepatitis is indirectly associated with reduced hepatic survival in NAFLD.[21,27] It drives fibrogenesis, a slow process of hepatic scar formation that can result in cirrhosis and its deadly complications such as liver failure, portal hypertension, and hepatocellular carcinoma. Consequently, clearance of steatohepatitis,[28] i.e., reversal to a normal liver or to steatosis without steatohepatitis – a condition not associated with increased hepatic morbidity or mortality – is expected to improve hepatic prognosis. Natural history studies are now available showing that patients with steatohepatitis but not those with steatosis only (i.e., nonNASH NAFLD) are the ones that progress to cirrhosis and liver-related outcomes. This forms the basis for "resolution of NASH" as a desirable outcome of therapy in the short-term; a concept widely embraced by the academic community and expressed in several scientific society endorsed position papers.[29,30] Based on the recently published recommendations from this workshop,[30] resolution of NASH with no worsening of fibrosis may be an acceptable surrogate endpoint suitable for a Phase III enrolling patients with NASH and

fibrosis. Based on recent data that have shown that fibrosis stage of 2 or more is related to liver-related mortality,[22] the "no worsening of fibrosis" should be no progression of one stage in fibrosis.

1.9.2. Primary endpoint for clinical outcome (postapproval confirmation)

The primary endpoint of the Long-term Treatment Period of the study is to evaluate the effect of elafibranor on all-cause mortality and liver-related clinical outcomes as measured by the time to first occurrence of any of the listed adjudicated events (clinical outcomes composite endpoint).

Primary endpoint events include overall mortality, progression to cirrhosis, and the full list of portal hypertension/cirrhosis related events (liver transplantation, model end stage liver disease (MELD) score ≥15, hepatocellular carcinoma (HCC), and hospitalization due to occurrence of hepatic encephalopathy, variceal bleeding, spontaneous bacterial peritonitis, uncontrolled ascites, hepatorenal syndrome, hepatopulmonary syndrome, and chronic gastrointestinal blood loss due to portal hypertensive gastropathy [provided that these lead to hospitalization or transfusion]).

Singh et al. recently provided a thorough meta-analysis of paired biopsy studies to obtain the most accurate estimate of the fibrosis progression rate in a large cohort of patients with NAFLD.[25] Over 2145.5 person-years of follow-up evaluation, 33.6% had fibrosis progression, 43.1% had stable fibrosis, and 22.3% had an improvement in fibrosis stage. Overall, the annual fibrosis progression rate in a population of patients with NAFLD who had stage 0 fibrosis at baseline was 0.07 stage/year compared to 0.14 stage/year in a population of patients with NASH. In another study of 108 patients, no significant difference in the proportion exhibiting fibrosis progression was found between those with NAFLD or NASH.[31] In the whole cohort, the mean annual rate of fibrosis progression was 0.08 stage/year.

Based on the literature, in patients with NASH and advanced fibrosis (F2-F3), the probability of developing cirrhosis can be estimated at 8% per year for fibrosis F3 and 6% per year for fibrosis F2.[21,22,23,24,25]

In conclusion, the difference in progression to cirrhosis, other liver-related events, and total deaths between treatment and control groups can be considered as a potential clinically meaningful outcome measure for clinical trials. This long-term outcome including progression to cirrhosis is considered acceptable,[30] and required in a postapproval study for treatments approved under conditional approval.

1.10. RATIONALE FOR STUDY DURATION

In accordance with the AASLD and EASL recommendations, 72-weeks of treatment have been defined for the first stage of the study in order to demonstrate the efficacy of elafibranor on resolution of NASH without worsening of fibrosis.

The estimated duration of the Long-term Treatment Period is based on a 7% probability of patients with NASH and moderate and advanced fibrosis (F2-F3) developing cirrhosis or other liver-related events as

determined from recently published data [21,22,23,24,25] and the available data of the mortality risk in this patient population.[32,33]

1.11. RATIONALE FOR SAFETY MONITORING

The safety of use of the dose of 120 mg/d of elafibranor during the proposed trial is supported by the chronic toxicity studies and previous Phase I and Phase II trials. Indeed, the toxicology package of elafibranor does not reveal any major safety concern, based on the conclusion that elafibranor-induced liver toxicity in rodents is not relevant to nonprimates (no evidence of liver toxicity in monkeys after 1 year but improvement of liver function markers) and humans (consistent improvement of liver function markers in all Phase II trials). These toxicology results and conclusions are on-line with the extensive literature on the liver effects of PPAR agonists.

An independent DSMB will be established in order to review the progress of the study and to perform a safety data review (as defined by the DSMB Charter) on a regular basis during the trial to protect patient welfare and preserve study integrity.

Knowing the risks associated with NASH and disease progression, specific attention will be paid to potential hepatotoxicity, liver-related and cardiovascular events.

Given the known effect of elafibranor on serum creatinine increase, special attention will be paid to all the renal safety markers (plasmatic or urinary parameters), including but not limited to albumin-creatine ration, cystatin C, neutrophil gelatinase-associated lipocalin (N-Gal), N acetyl β D-glucosaminidase β-NAG, kidney injury molecule-1 (KIM-1). Serum creatinine and creatinine clearance, and results of urinalysis (dipstick) will be reported at each visit, as well as blood urea nitrogen. The other markers (plasmatic or urinary) will be assayed in batch and will be reviewed on an ongoing basis through regular safety reviews by the DSMB which includes a nephrologist.

Assays of many other markers are scheduled in order to monitor liver function markers, cardiac safety markers, and to follow up the cardiovascular profile which is known to be at risk in NASH patients.

For cardiac safety, troponin-T and NT-ProBNP will be followed and reviewed on a regular basis by the DSMB. In addition, electrocardiogram (ECG) and blood pressure (BP) will be continuously controlled throughout the study.

Liver function will be monitored throughout the study, by assessment of liver enzymes, bilirubin (total or conjugated), alkaline phosphatase, and international normalized ratio (INR) reported at each visit.

In addition, even if no safety concern has been revealed in the previous clinical program, all the biological parameters that are known to be affected by PPAR agonists will remain monitored in the Phase III trials, such as hematological parameters, adiponectin, or homocysteine.

During the Long-term Treatment Period, patients will be monitored by clinical and biological assessment. A FibroScan® measurement and noninvasive markers assessment will be performed every 24 weeks, and if cirrhosis is suspected, a confirmation by liver biopsy will be performed.

For additional information see Investigator's Brochure.

2. TRIAL OBJECTIVES

2.1. PRIMARY OBJECTIVES

2.1.1. Surrogate endpoint -Interim analysis

To evaluate the efficacy of elafibranor QD for 72 weeks versus placebo on resolution of NASH without worsening of fibrosis.

- Resolution of NASH is defined as the disappearance of ballooning and disappearance or persistence of minimal lobular inflammation (grade 0 or 1) with an overall pattern of injury not qualifying for steatohepatitis.
- Worsening of fibrosis is evaluated using the NASH Clinical Research Network (CRN) fibrosis staging system and defined as progression of at least one stage.

2.1.2. Long-term endpoint

To evaluate the efficacy of elafibranor on clinical outcomes described as a composite endpoint composed of death to any cause, liver cirrhosis, and the full list of portal hypertension/cirrhosis related events:

- Liver transplantation
- MELD score ≥15
- HCC
- Hospitalization (as defined by a stay of 24 hours or greater) for new onset or recurrence of:
    - variceal bleed
    - hepatic encephalopathy
    - spontaneous bacterial peritonitis
    - uncontrolled ascites
    - hepatorenal syndrome
    - hepatopulmonary syndrome
    - chronic gastrointestinal blood loss due to portal hypertensive gastropathy (provided that these lead to hospitalization or transfusion).

2.2. KEY SECONDARY OBJECTIVE – INTERIM ANALYSIS

To assess histological changes after 72 weeks of treatment, at the time of interim analysis, on the following endpoint parameter:

- Percentage of patients with improvement of fibrosis of at least 1 stage according to NASH CRN scoring.

2.3. OTHER SECONDARY OBJECTIVES

- To assess histological changes after 72 weeks of treatment and follow-up biopsy on the following parameters:
    - percentage of patients with resolution of NASH without worsening of fibrosis (follow-up biopsy)
    - percentage of patients with improvement of fibrosis of at least 1 stage according to NASH CRN scoring
    - percentage of patients with at least 1 point improvement in histological scores (NASH CRN scoring: total NAS, steatosis, hepatic ballooning, lobular inflammation), fibrosis (NAFLD Ishak scoring system), or portal inflammation
    - percentage of patients with improvement of NAS score of at least 2 points
    - percentage of patients with at least a 1 point improvement in steatosis-activity-fibrosis (SAF) activity score
    - mean changes in NAS score, fibrosis, steatosis, hepatic ballooning, lobular inflammation, portal inflammation, SAF activity score
    - changes in area of fibrosis by morphometry
    - mean changes in fibrosis using NASH CRN and NAFLD Ishak scoring.
- To assess the following endpoints in elafibranor treated patients relative to placebo, at Week 72 and at the end of the Long-term Treatment Period:
    - cardiovascular events
    - liver-related death events
    - changes in liver enzymes and liver markers
    - changes in noninvasive markers of fibrosis and steatosis
    - changes in lipid parameters
    - variation in body weight
    - changes in insulin resistance and glucose homeostasis markers
    - changes in inflammatory markers
    - changes in cardiovascular risk profile as assessed by Framingham scores
    - changes in quality of life (36-Item Short-Form Health Survey [SF-36]) questionnaire).
- To assess Time to first occurrence of:
    - liver cirrhosis
    - death of any cause
    - any portal hypertension or cirrhosis related events.

2.4. EXPLORATORY OBJECTIVES

- To determine PK parameters of elafibranor (GFT505) and GFT1007 after 72 weeks of treatment for PK population analyses.

- To constitute a biobank for discovery and validation of biomarkers in NASH.

2.5. EXPLORATORY OBJECTIVES FOR F1 GROUP

- To explore the following endpoints in elafibranor treated F1 patients in the exploratory group relative to placebo at Week 72 and at the end of the Long-term Treatment Period:
    - resolution of NASH without worsening of fibrosis.
    - percentage of patients with at least 1 point reduction in NASH CRN fibrosis score and NAFLD Ishak score.
    - percentage of patients with at least 1 point improvement in NAS, steatosis, ballooning, lobular inflammation, or portal inflammation.
    - percentage of patients with improvement of NAS score of at least 2 points.
    - percentage of patients with at least a 1 point improvement in SAF activity score.
    - mean changes in NAS score, fibrosis (using NASH CRN or NAFLD Ishak scoring system), steatosis, hepatic ballooning, lobular inflammation, portal inflammation, and SAF activity score.
    - changes in area of fibrosis by morphometry.
- To explore the following endpoints in F1 patients at Week 72 and after the Long-term Treatment Period:
    - composite endpoint as described in Section 2.1.2.
    - cardiovascular events.
    - changes in liver enzymes and liver markers.
    - changes in noninvasive markers of fibrosis and steatosis.
    - changes in lipid parameters.
    - variation in body weight.
    - changes in insulin resistance and glucose homeostasis markers.
    - changes in inflammatory markers.
    - changes in cardiovascular risk profile as assessed by Framingham scores.
    - changes in quality of life (SF-36 questionnaire).
- To determine PK parameters of elafibranor (GFT505) and GFT1007 after 72 weeks of treatment.
- To assess the tolerability and safety.

2.6. SAFETY SECONDARY OBJECTIVES

To assess the tolerability and safety of once a day administration of oral doses of elafibranor 120 mg description of:

- SAE, AE, physical examination, vital signs, medical history, ECG
- hematological parameters
- liver function parameters
- renal function parameters (including urinalysis)

- cardiac function parameters
- metabolic parameters
- other biochemical safety markers.

3. TRIAL DESIGN

This is a Phase III, randomized, double-blind, parallel groups, placebo-controlled study, evaluating the efficacy and safety of elafibranor 120 mg QD versus placebo in an adult NASH population with fibrosis. The first double-blind 72-week Treatment Period will assess the efficacy and safety of elafibranor on the resolution of NASH without worsening of fibrosis at the intermediate efficacy analysis, followed by a Long-term Treatment Period to assess the prevention of mortality all cause, progression to cirrhosis, and to the full list of portal hypertension/cirrhosis related events (see Section 2.1.2). The study will terminate upon the 456th patient (excluding exploratory F1 group [see below]) experiencing an event listed in the composite endpoint for long term efficacy evaluation.

It is planned to randomize patients to either active or placebo treatment in a 2:1 ratio, stratified by type 2 diabetes, gender (with a capping of women to 40%), and fibrosis stage. Additional patients with fibrosis stage 1 (10% of sample size calculated for the F2 and F3 patients) and high risk for progression of NASH will also be enrolled for exploratory purposes.

3.1. NUMBER OF PATIENTS

It is planned to randomize 2022 F2/F3 patients to either active (1348 patients) or placebo (674 patients) treatment in a 2:1 ratio up to 202 additional patients (a maximum level of 10% of the F2/F3 enrolled patients) with fibrosis stage of 1 and high risk for progression of NASH (NAS ≥5, F1 patients with 2 of the following conditions: persistent elevated ALT, obesity defined by a body mass index (BMI) ≥30, metabolic syndrome [National Cholesterol Education Program's Adult Treatment Panel III {NCEP ATP III definition}], type 2 diabetes, or HOMA-IR >6) will also be enrolled, and followed as an exploratory group. The F1 patients will not be included in the primary interim and final analysis or in the sample size calculation (detailed in Section 9.7). As such a total of 2224 patients will be enrolled, including the exploratory F1 group.

3.2. METHOD OF ASSIGNING PATIENT TO TREATMENT GROUP

Patients who satisfy all eligibility criteria will be randomly allocated to one of the following groups in a 2:1 ratio:

- Elafibranor 120 mg
- Placebo.

Randomization to treatment will be stratified to ensure balance of treatment allocation by the following 3 factors:

- Type 2 diabetes (yes, no)
- Gender (male, female) (with a capping of women to 40%)
- Fibrosis stage (F1, F2, F3) (capped to 202 F1 patients).

Treatment assignments will be made using an interactive voice/web response system (IXRS).

3.3. DOSE ADJUSTMENT CRITERIA

Not applicable. Patients will be randomized to a fixed dose with no allowance for dose adjustment.

3.4. DURATION OF STUDY PARTICIPATION

The estimated duration of the study will be approximately 72 months, based on 456 patients experiencing an event described in Section 2.1.2 at an assumed annual rate event of 7%. However, this may be redefined according to the actual occurrence of events (described in Section 2.1.2) during the confirmatory part of the study (Long-term Treatment Period).

3.5. STUDY PERIODS

The study will comprise 3 periods. The Screening Period (-12 to -1 weeks) will precede a 72-week double-blind First Treatment Period and a Long-term Treatment Period up to the occurrence of a prespecified number of events.

Study procedures are summarized in Table 1, Table 2, and Figure 1.

Schedule:

- Week -12 to Week -1 prior to Randomization: Screening Period (screening visits SV1 to SPV).
- Week 0 to Week 72: First Treatment Period with Elafibranor or placebo for 72 weeks (visits V1 to V7).
- Week 72 to end of study (EOS): Long-term Treatment Period with elafibranor or placebo until 456 patients experience an event listed in Section 2.1.2 (visits V8 to Vn).

3.6. SCREENING PERIOD

3.6.1. Screening visits SV1 (Week -12 to Week -8) and SV2 (Week -12 to Week -4):

The following screening procedures will be performed for all potential patients at SV1 conducted between Week -12 and Week -8 prior to Randomization:

- Signature of informed consent witnessed by the Investigator or designated person.
- Patient number allocation via IXRS.
- Check medical history/demographics.
- Check inclusion/exclusion criteria (described in Section 4).
- Physical examination (described in Section 6.2.1).

- Adequate diet recommendations (described in Section 5.1.1 and APPENDIX II: Adequate diet and lifestyle recommendations), alcohol restrictions (described in Section 5.1.2), and tobacco habits.
- Record vital signs (described in Section 6.2.2).
- Record height, weight, and waist circumference.
- Check concomitant/prior medication (within 30 days prior to Screening) (described in Section 7.10 and APPENDIX III: Permitted/Non-permitted medication)
- Check if a liver biopsy with confirmed NASH and fibrosis is available, and, if so send sample for central confirmation of NASH diagnosis (described in Section 6.1.1.2). This historical diagnostic biopsy should be obtained within 6 months prior to the planned Randomization Visit V1.
- Check AEs from time of Informed Consent Form (ICF) signature (described in Section 6 and Section 8).

The Screening biological assessment (SB1 will be scheduled at SV1.

If no diagnostic liver biopsy (within 6 months of V1) is available at visit SV1, an additional SV2 visit will be booked at least Week -4 (period between Screening and Week -4) prior to the planned Randomization V1.

The following biological assessments (detailed in Table 2) will be performed at SB1:

- Blood samples (described in Table 2).
- Whole blood, plasma & serum bank samples (only if additional genetic and biomarker ICF signed).
- Urinalysis dipstick.
- Urinary pregnancy test (for women of childbearing potential only [WOCBP]).

For DILI adjudication, in order to define an adequate baseline value for the liver parameters (AST, ALT, total bilirubin, INR), at least 2 consecutive assessments in at least 8 weeks apart between visit SV1 and V1 should be performed. Visits SV1 and V1 should be scheduled according to this requirement.

If needed, a retesting of abnormal HbA1c, estimated glomerular filtration rate (eGFR) or creatine phosphokinase (CPK) results or additional testing of hepatitis C virus (HCV) RNA, may be performed during the screening window to determine the eligibility for the study as described in exclusion criteria 5, 13, 31, and 32 (see Section 4.2 and Section 3.11).

At visit SV1, preliminary entrance criteria will be reviewed. Potentially eligible patients will be asked if they agree to participate in the study and sign the ICF. Each patient who will have signed the ICF will be allocated a patient number composed of 7 digits which is generated by the IXRS.

- First 3 digits corresponding to the ISO numeric country code (this number will be predefined),
- Next 2 digits corresponding to the site number (this number will be predefined),
- Last 2 digits corresponding to the numerical order of the patient entry at the study site.

A specific IXRS procedure manual will be provided to the Investigator.

3.6.2. Screening Visit SV2 (liver biopsy if required, Week -12 to Week -4):

If no diagnostic liver biopsy (within 6 months of V1) is available at visit SV1, an additional SV2 visit will be booked by at least Week -4 for a liver biopsy to be performed (described in Section 6.1.1.1). Blood samples for coagulation (detailed in Table 2) will be taken and tested at a local laboratory prior to the liver biopsy. Liver biopsy samples will be sent for central confirmation of NASH diagnosis (described in Section 6.1.1.2).

During this visit AEs (from the time of signing the ICF) will also be checked (described in Section 6 and Section 8).

3.6.3. Screening Phone Visit SPV (Week -1):

Upon receipt of the NASH diagnosis confirmation and the SB1 or any retesting/additional testing results from the central laboratory, the Investigator should check the eligibility with inclusion/exclusion criteria.

If patient meets all inclusion criteria and none of the exclusion criteria (clinical, histological, and biological ones), the Investigator will inform the patient of his/her inclusion/noninclusion status by a phone call within 1 week prior to the Randomization Visit V1. In case of ineligibility, the patient should be contacted as soon as possible.

3.7. FIRST TREATMENT PERIOD (WEEK 0 TO WEEK 72)

Efficacy of elafibranor versus placebo on resolution of NASH without worsening of fibrosis will be evaluated in this first period treatment of 72 weeks.

The NASH will be evaluated for inclusion by a centrally-read liver biopsy taken within 6 months prior to randomization (if no historical biopsy is available for NASH diagnosis, a liver biopsy will be performed during the Screening Period) with:

- Presence of NASH, with at least a score of 1 in each component of the NAS score (steatosis scored 0 to 3, ballooning degeneration scored 0 to 2, and lobular inflammation scored 0 to 3) AND NAS score ≥4.
- Fibrosis stage 2 and 3.

A group of patients (n=202, 10% of each group) with F1 fibrosis, NAS ≥5, and concomitant cardiometabolic comorbidities, which are associated with rapid progression of the disease (listed in Section 3.1), will also be enrolled and followed as an exploratory group.

During these first 72 weeks of treatment, visits will be scheduled every 12 weeks. Clinical and biological evaluation will be performed during this First Treatment Period.

At the end of the 72-week treatment period, a biopsy will be performed for all the patients under treatment in order to evaluate the effect of elafibranor on the liver histology.

When 1023 patients (F2-F3) complete Week 72 (or discontinue early from the study), an interim analysis will be performed and potentially filed for initial market approval under Subpart H or conditional approval, (see Section 9.8.1 for details).

During the First Treatment Period the patients will return to the site for visits every 12 weeks (±1 week) from the Randomization Visit (V1); however the maximum time period between visits is to be 96 days due to the study drug supply provided to the patient.

A diagnosis of any event listed in the primary composite endpoint described in Section 1.9.2 will result in the permanent discontinuation of study drug and discontinuation from the study, following an end of study treatment (EOT) Visit as described in Section 3.9 and Section 5.2.2).

3.7.1. Randomization Visit V1 (Week 0):

Eligible patients will return to the site at the Randomization Visit V1 and then every 12 weeks in the First Treatment Period of the study until the first 72 weeks of treatment (V7) (interim analysis). The patient will be contacted at least 1 week before each visit to be reminded of procedures and investigational product (IP) return.

If the patient is eligible, the Investigator will register the patient for randomization in the IXRS, prior to any other study procedures. If the system confirms the randomization, it will provide the Investigator with a treatment number for the patient.

The following will be performed only at V1:

- Check inclusion/exclusion criteria (detailed in Section 4).
- Randomization to one of 2 treatments groups (elafibranor or placebo in 2:1 ratio, detailed in Section 3.2) via the IXRS.

3.7.2. First Treatment Period visits V1 to V7 (Week 0 to Week 72):

The following procedures will be performed at each of the 12-week visits from V1 to V7:

- IXRS registration
- Physical examination (described in Section 6.2.1)
- Record vital signs and weight (described in Section 6.2.1 and Section 6.2.2)
- Confirmation of adequate diet and lifestyle compliance (described in Section 5.1.1 and APPENDIX II: Adequate diet and lifestyle recommendations), alcohol restrictions (described in Section 5.1.2), and tobacco habits

- Check concomitant/prior medication (described in Section 7.10 and APPENDIX III: Permitted/Non-permitted medication)
- Quality of life assessment (V1, V3, V5, and V7, only; described in Section 6.2.5)
- Check AEs (all visits) and occurrence of any clinical outcome (from V2 onwards) (described in Section 6 and Section 8)
- Study placebo or drug dispensation (described in Section 7.4)
- Blood samples (described in Table 2)
- Plasma & serum bank samples (only if additional genetic and biomarker ICF signed)
- Urinalysis and urinary dipstick (described in Table 2)
- Urinary pregnancy test (for WOCBP only)
- Record waist circumference (V1, V3, V5, and V7, only).
- 12-lead ECG (V1, V4, and V7, only; described in Section 6.2.3)
- FibroScan (V1 and V7 only, described in Section 6.2.4)
- Drug accountability (every visit from V2).

Additional procedures to be performed at V7 are:

- PK blood sampling (2 hours and 5 hours 45 minutes postdose, see Section 6.1.4).
- Liver biopsy (described in Section 6.1.1). **Note:** the liver biopsy may be performed at V7 or during a separate visit that occurs within the V7 window of 72 weeks ± 1 week from V1. Liver biopsy samples will be sent for central histological evaluation.
- Blood samples for coagulation taken (platelets count and prothrombin time [PT] [INR]; described in Table 2) and tested at a local laboratory prior to the liver biopsy.

3.8. LONG-TERM TREATMENT PERIOD

The main objective to be evaluated during the Long-term Treatment Period will be the prevention of progression to cirrhosis, or to portal hypertension/cirrhosis related events (as described in Section 1.9.2.

After the 72-week biopsy, patients will continue in the double-blind Long-term Treatment Period, receiving the same treatment as assigned at V1 (elafibranor 120 mg or placebo). Patients will be monitored by notably measuring the appearance of cirrhosis (based on FibroScan measurement associated with biological and/or clinical assessments and confirmed by biopsy).

At or after the 72-week biopsy, a diagnosis of any event listed in the primary composite endpoint described in Section 1.9.2 will result in the permanent discontinuation of study drug and discontinuation of the study following the EOT Visit (as described in Section 3.9 and Section 5.2.3).

3.8.1. Long-term Treatment Period visits (V8 to Vn)

Patients will return to the site every 24 weeks during the Long-term Treatment Period. The patient will be contacted at least 1 week before each visit to be reminded of procedures and IP return.

The following procedures will be performed at each visit from V8 to Vn:

- IXRS registration
- Physical examination (described in Section 6.2.1)
- Record vital signs and weight (described in Section 6.2.1 and Section 6.2.2)
- Confirmation of adequate diet and lifestyle compliance (described in Section 5.1.1 and APPENDIX II: Adequate diet and lifestyle recommendations), alcohol restrictions (described in Section 5.1.2), and tobacco habits
- Check concomitant/prior medication (described in Section 7.10 and APPENDIX III: Permitted/Non-permitted medication)
- Quality of life assessment (V8, V9, V11, and 48 weekly thereafter Section 6.2.5)
- Check AEs and occurrence of any clinical outcome (described in Section 6 and Section 8)
- Study placebo or drug dispensation (described in Section 7.4, with the exception of the final Vn visit)
- Blood samples (described in Table 2)
- Plasma & serum bank samples (only if additional genetic and biomarker ICF informed consent signed)
- Urinalysis and urinary dipstick (described in Table 2)
- Urinary pregnancy test (for WOCBP only)
- Record waist circumference
- 12-lead ECG (every 48 weeks from V9; described in Section 6.2.3)
- FibroScan (described in Section 6.2.4)
- Drug accountability
- Liver biopsy (at approximately 4 years [V13], and in case of suspected liver cirrhosis, described in Section 6.1.1). Liver biopsy samples will be sent for central histological evaluation
- Blood samples for coagulation taken (platelets count and PT [INR]; described in Table 2) and tested at a local laboratory prior to the liver biopsy.

3.8.2. Long-term Treatment Period phone visits (PV1 to PVn)

Phone visits will be scheduled every 24 weeks starting 12 weeks after Visit 7 for data collection on clinical outcomes, safety and IP compliance control. If any information during this phone contact requires a visit, the Investigator may decide to perform an unscheduled visit (described in Section 3.11.2). IXRS registration will be performed for each phone visit.

3.9. END OF STUDY TREATMENT VISIT

At the EOS (upon occurrence of the expected number of events), all patients will be asked to stop treatment and undergo an EOT Visit 30 days after the final administration of study drug.

All patients who permanently discontinue their study medication will undergo an EOT Visit 30 days after the final administration of study drug. Patients who permanently discontinue study drug for any reason other than an event listed in the primary composite endpoint for long-term efficacy described in Section 1.9.2 will remain, upon agreement, in the study after the EOT Visit and be followed up to evaluate efficacy outcomes and safety through 24 weekly phone call visits as described in Section 3.10 and Section 5.2.

If a patient discontinues from the study, every attempt should be made to have the patient return to the site and complete the EOT Visit 30 days after the final administration of study drug. For details of the EOT Visit see Table 1, Table 2, and Figure 1.

The following procedures will be performed at the EOT Visit:

- IXRS registration
- Physical examination (described in Section 6.2.1)
- Record vital signs and weight (described in Section 6.2.1 and Section 6.2.2)
- Check concomitant/prior medication (described in Section 7.10 and APPENDIX III: Permitted/Non-permitted medication)
- Quality of life assessment (described in Section 6.2.5)
- Check AEs and occurrence of any clinical outcome(described in Section 6 and Section 8)
- Blood samples (described in Table 2)
- Plasma & serum bank samples (only if additional genetic and biomarker ICF informed consent signed)
- Urinalysis and urinary dipstick (described in Table 2)
- Urinary pregnancy test (for WOCBP only)
- Record waist circumference
- 12-lead ECG (described in Section 6.2.3)
- Drug accountability.

Patients discontinuing study drug or discontinuing the study will be asked to return all used and unused study treatments at the EOT Visit.

3.10. FOLLOW-UP FOR PATIENTS WHO HAVE PERMANENTLY DISCONTINUED STUDY DRUG

Patients who have permanently discontinued study drug due to an event listed in the primary composite endpoint for long-term efficacy described in Section 1.9.2 will be discontinued from the study following the EOT Visit and have no further follow-up.

Patients who have permanently discontinued study drug for any other reason will remain, upon agreement, in the study and will be followed up with 24 weekly phone visits (±2 weeks from EOT Visit) following the EOT Visit to report safety, diagnosis of cirrhosis and occurrence of clinical outcomes (as listed below)

including liver and cardiovascular events until EOS or the occurrence of an event listed in the primary composite endpoint for long-term efficacy (described in Section 1.9.2), whichever is sooner.

The following procedures will be performed during the follow-up phone visit for patients who have permanently discontinued study drug:

- IXRS registration.
- Reporting of safety information regarding:
  - any new AEs
  - resolution of previous AEs
  - change in severity of existing AEs
  - occurrence of any cardiovascular events
  - occurrence of diabetes (for patients not previously diagnosed with diabetes)
  - worsening of diabetes (for patients previously diagnosed with diabetes).
- Reporting of any change in diet and life style factors
- Reporting of any change (quantitative or qualitative) in therapies post study drug discontinuation
- Reporting of cirrhosis diagnosis (patient to be asked if they have had any histological confirmation of cirrhosis)
- Reporting of any of the following events (primary composite endpoint for long-term efficacy evaluation):
  - liver transplantation
  - MELD score ≥15
  - HCC
  - hospitalization (as defined by a stay of 24 hours or greater) for new onset or recurrence of:
    - variceal bleed
    - hepatic encephalopathy
    - spontaneous bacterial peritonitis
    - uncontrolled ascites
    - hepatorenal syndrome
    - hepatopulmonary syndrome
    - chronic gastrointestinal blood loss due to portal hypertensive gastropathy (provided that these lead to hospitalization or transfusion).
  - death due to any cause.

3.11. OPTIONAL VISITS

3.11.1. Retesting screening visits

Upon receipt of results from biological assessment done at SV1, and in case a retesting or additional testing is needed according to the selection criteria, an additional visit will be scheduled according to the recommended timeframe for retesting.

Permitted retesting or additional testing in case of abnormal value at SV1 are:

- CPK: can be repeated prior to Randomization (V1) within 1 to 2 weeks after initial test.
- eGFR measurement: can be repeated prior to Randomization (V1) within the following timeframe: minimum 4 weeks after initial test and maximum 2 weeks prior to planned Randomization.
- HCV RNA testing, in case positive HVC Ab test: required latest 2 weeks prior to Randomization (V1).
- HbA1c: can be repeated at the latest 2 weeks prior to Randomization (V1).

3.11.2. Unscheduled visits

An unscheduled visit is defined as any visit to the study unit outside of the protocol-evaluation timepoints where the patient is seen by study unit personnel, e.g., when follow-up assessments are required for safety reasons or when repeat measurements are required out of the screening period (either to confirm a measurement or in case of errors, measuring device failure, etc).

Unscheduled visits will be needed for patients who may require further follow-up due to safety.

3.12. EXPLORATORY/ANCILLARY SUBSTUDY

Exploratory substudies might be performed during the study in sites that have the corresponding capability. Specific study documents will be prepared and Institutional Review Board (IRB)/ Independent Ethics Committee (IEC) and authority approvals shall be obtained when applicable.

4. PATIENT SELECTION

A patient will be eligible for the study only if all of the following criteria apply:

4.1. INCLUSION CRITERIA

Patients must meet all of the following inclusion criteria to be eligible for enrollment in the trial:

1. Males or females aged from 18 to 75 years inclusive at first Screening Visit.
2. Must provide signed written informed consent and agree to comply with the study protocol.
3. BMI ≤45 kg/m².
4. Females participating in the study must either not be of childbearing potential (hysterectomy, bilateral oophorectomy, medically documented ovarian failure, or >50 years of age with cessation of menses for at least 12 months due to ovarian failure) or using efficient double contraception: hormonal contraception (including patch, contraceptive ring, etc), intra-uterine device, or other mechanical contraception method + condom or diaphragm or spermicide for the full duration of the study and for 1 month after the end of treatment.
5. Histological confirmation of steatohepatitis on a diagnostic liver biopsy by central reading of the slides (biopsy obtained within 6 months prior to Randomization or during the Screening Period) with at least 1 in each component of the NAS score (steatosis scored 0-3, ballooning degeneration scored 0-2, and lobular inflammation scored 0-3).
6. NAS score ≥4.
7. Fibrosis stage of 1 or greater and below 4, according to the NASH CRN fibrosis staging system.

   For patients with fibrosis stage 1, only patients at high risk of progression will be included meaning with a NAS score >5 and 2 of the following conditions: persistent elevated ALT, obesity defined by a BMI ≥30, metabolic syndrome (NCEP ATP III definition), type 2 diabetes, or HOMA-IR ≥6.
8. Patients agree to have 1 liver biopsy during the Screening Period for diagnostic purpose (if no historical biopsy within 6 months before Randomization is available), 1 liver biopsy after 72-weeks of treatment for assessment of the treatment effects on NASH, as well as another in case of suspicion of cirrhosis, (to have a histological confirmation), and a final liver biopsy after approximately 4 years of treatment (V13), unless a biopsy has already been performed within the year.
9. Stable dose of vitamin E (>400 IU/day), polyunsaturated fatty acids (PUFAs, >2 g/day), or ursodeoxycholic acid from at least 6 months prior to diagnostic liver biopsy.
10. For patients with type 2 diabetes, glycemia must be controlled. If glycemia is controlled by anti-diabetic drugs, no change is allowed within 6 months prior to diagnostic liver biopsy, under the following conditions:
    - No change in dose for patients treated by GLP-1 agonists

- No qualitative change (i.e. implementation of a new anti-diabetic therapy) for patients treated by metformin, dipeptidyl-peptidase 4 inhibitors, sodium/glucose cotransporter 2 (SGLT2) inhibitors, sulfamides, or insulin.

4.2. EXCLUSION CRITERIA

Patients who meet any of the following criteria will be excluded from entering the study:

1. Known heart failure (Grade I to IV of New York Heart Association classification).
2. History of efficient bariatric surgery within 5 years prior to Screening.
3. Uncontrolled hypertension during the Screening Period despite optimal antihypertensive therapy.
4. Type 1 diabetes patients.
5. Patients with decompensated diabetes (HbA1c >9.0%). If abnormal at the first Screening Visit, the HbA1c measurement can be repeated at the latest 2 weeks prior to Randomization. A repeated abnormal HbA1c (HbA1c >9.0%) leads to exclusion.
6. Patients receiving thiazoledinediones (pioglitazone, rosiglitazone), unless the drug was discontinued at least 6 months before the diagnostic liver biopsy.
7. Patients with a history of clinically significant acute cardiac event within 6 months prior to Screening such as: acute cardiovascular episode, stroke, transient ischemic attack, or coronary heart disease (angina pectoris, myocardial infarction, revascularization procedures).
8. Weight loss of more than 5% within 6 months prior to Randomization.
9. Compensated and decompensated cirrhosis (clinical and/or histological evidence of cirrhosis). Notably, NASH patients with fibrosis stage = 4 according to the NASH CRN fibrosis staging system are excluded.
10. Current or recent history (<5 years) of significant alcohol consumption. For men, significant consumption is typically defined as higher than 30 g pure alcohol per day. For women, it is typically defined as higher than 20 g pure alcohol per day. See APPENDIX IV: Alcohol comparison table.
11. Patients who have donated blood or blood products within 1 month prior to Screening or who plan to donate blood or blood products at any time during the trial and in the 2 months following the end of the study.
12. Pregnant or lactating females or females planning to become pregnant during the study period.
13. Other well documented causes of chronic liver disease according to standard diagnostic procedures including, but not restricted to:
    - Positive hepatitis B surface antigen (HBsAg)
    - HCV RNA
    - Suspicion of drug-induced liver disease
    - Alcoholic liver disease
    - Autoimmune hepatitis

- Wilson's disease hemochromatosis
- Primary biliary cirrhosis, primary sclerosing cholangitis
- Genetic hemochromatosis
- Known or suspected HCC
- History or planned liver transplant, or current MELD score >12.

14. Where applicable, patients not covered by Health Insurance System and/or not in compliance with the recommendations of National Law in force.
15. Patients who cannot be contacted in case of emergency.
16. Known hypersensitivity to the investigation product or any of its formulation excipients.
17. Patients with previous exposure to elafibranor.
18. Patients who are currently participating in, plan to participate in, or have participated in an investigational drug or medical device trial within 30 days or five half-lives, whichever is longer, prior to Screening.

Concomitant medications (see APPENDIX III: Permitted/Non-permitted medication):

19. Fibrates are not permitted from 2 months before Randomization. Patients that used statins or ezetimibe before Screening may participate if the dosage has been kept constant for at least 2 months prior to Screening.
20. Currently taking drugs that can induce steatosis/steatohepatitis including, but not restricted to: corticosteroids (parenteral & oral chronic administration only), amiodarone (Cordarone), tamoxifen (Nolvadex), and methotrexate (Rheumatrex, Trexall), which are not permitted 30 days prior to Screening.
21. Currently taking any medication that could interfere with study medication absorption, distribution, metabolism, or excretion or could lead to induction or inhibition of microsomal enzymes, e.g. indomethacin, which are not permitted from Randomization.

Associated illnesses or conditions:

22. Any medical conditions that may diminish life expectancy to less than 2 years including known cancers.
23. Evidence of any other unstable or, untreated clinically significant immunological, endocrine, hematological, gastrointestinal, neurological, neoplastic, or psychiatric disease.
24. Mental instability or incompetence, such that the validity of informed consent or ability to be compliant with the study is uncertain.

In addition to the above criteria, patient should not present any of the following biological exclusion criteria:

25. Positive anti-human immunodeficiency virus (HIV) antibody.

26. AST and/or ALT >10 x the upper limit normal (ULN).
27. Total bilirubin >25 µmol/L (1.5 mg/dL).
28. INR >1.4.
29. Platelet count <100,000/mm^3.
30. Serum creatinine levels >135 µmol/L (>1.53 mg/dL) in males and >110 µmol/L (1.24 mg/dL) in females.
31. Significant renal disease, including nephritic syndrome, chronic kidney disease (defined as patients with markers of kidney damage or eGFR of less than 60 ml/min/1.73 m^2). If abnormal at the first Screening Visit, the eGFR measurement can be repeated prior to the Randomization within the following timeframe: minimum 4 weeks after initial test and maximum 2 weeks prior to planned Randomization. A repeated abnormal eGFR (less than 60 ml/min/1.73 m^2) leads to exclusion.
32. Unexplained serum CPK >3 x the ULN. In case of explained elevated CPK >3 x the ULN, the measurement can be repeated prior to Randomization. In this case, retest should be performed within 1 to 2 weeks after initial test. A CPK retest >3 x ULN leads to exclusion.

5. TRIAL PROCEDURES

The procedures performed at each visit are summarized in the study schedules (see Table 1, Table 2, and Figure 1) and in Section 3.

The Investigator will be asked, whenever possible, to schedule patient visits at the same time of day for each patient. A patient may be seen at any time for reasons of safety.

During each visit, lifestyle and study recommendations will be repeated, vital signs will be measured, and the patient will be queried in the form of an open question regarding new or continuing events.

Procedures for premature discontinuation after SV1 are described in Section 5.2.

5.1. LIFESTYLE RECOMMENDATIONS AND STUDY RECOMMENDATIONS

5.1.1. Standard diet and exercise recommendations

Standard diet and exercise recommendations given by the Investigator during SV1 will have to be maintained throughout the study. These recommendations will be based on Therapeutic Lifestyle Change (TLC) counseling (or local equivalent) according to NCEP ATP III guidelines. The essential components of TLC and the macronutrient recommendations for the TLC diet are detailed in APPENDIX II: Adequate diet and lifestyle recommendations.

Assessment of dietary and lifestyle compliance will occur at each visit by asking the patient 2 questions to confirm if they have remained compliant to the diet and lifestyle recommendations ("Have you remained compliant to the recommended diet since the last visit?" and "Have you remained compliant to the recommended physical activity since the last visit?". A yes/no response will be recorded in the electronic care report form (eCRF).

5.1.2. Dietary and fluid restrictions

The following restrictions should be applied to patients in this trial from SV1 through to the end of the study:

- Patients will be required to fast (no food or drink other than water) for at least 12 hours prior to all blood sampling. As such, patients should not consume any breakfast or take any medication (including study medication) in the morning prior the blood sampling. In case the patients do not fast before a visit, a new appointment will be scheduled within 2 days.
- On each study visit day, study treatment will be taken in fasted conditions after the blood sampling (which corresponds to the day of the visit).
- During the 48 hours preceding each study visit, patients should not perform strenuous exercise.

- Patients are to avoid consumption of dietary supplements such as anti-oxidant (including, but not limited to Vitamin A, Vitamin C, provitamin A, selenium, and polyphenol).
- Alcohol consumption should be limited during the study duration and registered in the eCRF. Alcohol consumption of more than 20 g per day for women and 30 g per day for men is considered abusive (see APPENDIX IV: Alcohol comparison table). A standard drink is equal to 14.0 grams (0.6 ounces) of pure alcohol. Generally, this amount of pure alcohol is found in:
    - 12-ounces/350 ml of beer (5% alcohol content)
    - 5-ounces/150 ml of wine (12% alcohol content)
    - 1.5-ounces/50 ml (40% alcohol content) distilled spirits or liquor (e.g., gin, rum, vodka, whiskey).

Concomitant therapy is restricted and any change to treatment or introduction of a new treatment should be discussed with the Investigator before doing so (see Section 7.10 and APPENDIX III: Permitted/Non-permitted medication).

5.2. PATIENT WITHDRAWAL AND PATIENT TREATMENT DISCONTINUATION RULES

5.2.1. Handling of patient withdrawal

Patients will be informed that they have the right to discontinue the study at any time, for any reason, without affecting future management and treatment.

5.2.2. Permanent discontinuations of study drug

In some instances, it may be necessary for a patient to permanently discontinue study drug. The patient may be discontinued from study drug at any time at the discretion of the Investigator or Sponsor for safety, behavioral, or administrative reasons. In keeping with the ITT analysis, the patient will not be permanently discontinued from the study.

The reason for permanent discontinuation of study drug should be documented in the eCRF and the Medical Monitor informed. If the discontinuation of study drug is due to an AE, the event should be documented in the eCRF.

Some possible reasons that may lead to permanent early study drug discontinuation include:

- Occurrence of any event listed in the composite endpoints for long-term efficacy evaluation (see Section 1.9.2)
- In the opinion of the Investigator, any AE, SAE (described in Section 8), or significant change in a laboratory value that warrants permanent discontinuation of study drug therapy. Investigators are advised to call the Medical Monitor prior to making such a decision
- Occurrence of repeated hypoglycemic episodes without possibility for a down titration of background therapy that may put the patient at risk with continued participation

- Non-permitted concomitant medication (described in Section 7.10 and APPENDIX III: Permitted/Non-permitted medication)
- Female patients who are pregnant (see Section 8.6.1) or are breastfeeding or who do not agree to use a reliable method of birth control during the study will be permanently discontinued from study drug
- Non-compliance with the study treatment
- Uncooperative patient
- The patient requests to stop study drug permanently.

Patients permanently discontinued from study drug will be requested to stop taking study drug and attend an EOT Visit 30 days after the last administration of study drug (described in Section 3.9).

If the study drug is discontinued due to the occurrence of any event listed in the composite endpoints for long-term efficacy evaluation (see Section 1.9.2), the patient will also be discontinued from the study with no further follow-up after the EOT Visit.

If the study drug is discontinued due to any reason other than the occurrence of any event listed in the composite endpoints for long-term efficacy evaluation, the patient will undergo, if agreed, 24 weekly telephone visits (described in Section 3.10) after the EOT Visit until the EOS or the occurrence of any event listed in the primary composite endpoints for long-term efficacy evaluation (see Section 1.9.2), whichever is sooner.

5.2.3. Patient discontinuation from the Study

Patient discontinuation prior to the patient's completion of the study is expected to be low, occurring if the patient withdraws consent, or if enrollment in any other clinical trial involving an investigational product, or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study, occurs.

At the time of discontinuing from the study, the Medical Monitor and IXRS should be contacted, and, if possible, an EOT Visit should be conducted (see Section 3.9). The patient will be permanently discontinued from the study at that time with no further follow-up and the date the patient is withdrawn from the study and the reason for withdrawal should be appropriately documented in the eCRF. During the study close-out period, survival status will be collected within legal and ethical boundaries for all patients randomized who withdrew participation from the study.

Where possible, patients withdrawn from the study will be followed until resolution of all their SAEs or until the unresolved SAEs are judged by the Investigator to have stabilized.

5.2.4. Patients lost to follow-Up

A patient would be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. Site personnel are expected to make diligent attempts to contact patients who fail to return for a scheduled visit or were otherwise unable to be followed up by the site. Vital status will be collected within legal and ethical boundaries for all patients randomized, including those who did not get study drug. Vital status will be searched in public sources during the study close-out period. If vital status is determined, the patient will not be considered lost to follow-up.

5.2.5. Replacement

No patient replacements are permitted in this study.

5.2.6. Premature discontinuation of the study

Premature termination of this clinical trial may occur because of a Regulatory Authority decision, change in opinion of the IRB/IEC, drug safety problems, DSMB recommendations, or at the discretion of the Sponsor. In addition, the Sponsor retains the right to discontinue development of the study treatment at any time.

The Sponsor reserves the right to discontinue the trial prior to inclusion of the intended number of patients, but intends only to exercise this right for valid scientific or administrative reasons. After such a decision, the Investigator must contact all participating patients within a reasonable period of time. As directed by the Sponsor, all trial materials must be collected and all eCRFs completed to the greatest extent possible.

Furthermore, the Investigator can decide to prematurely discontinue the study. In that event, the Investigator must notify the Sponsor immediately of his/her decision and give the reason in writing. Prompt compliance with this requirement is essential so that the Sponsor may comply with its regulatory obligations.

In all cases, ethics committee (IRB/IEC) and Health Authorities should be informed.

If the Investigator decides to prematurely discontinue the study, all test articles, eCRFs, and related study materials must be returned to the Sponsor.

6. ASSESSMENTS

6.1. EFFICACY AND SAFETY ASSESSMENTS

6.1.1. Histological assessments

A liver biopsy (see Section 6.1.1.1 for recommendations) will be performed at baseline, after 72 weeks of treatment, in case cirrhosis is suspected at any interim visit during the Long-term Treatment Period (based on FibroScan **and** biological assessments) and after approximately 4 years of treatment (V13) unless a biopsy has been performed within the previous year.

A Laboratory Manual will be provided to each trial site. The manual will outline the collection process, and shipping requirements for the specific central laboratory.

6.1.1.1. Recommendations related to liver biopsy

Before performing a percutaneous liver biopsy, there must be a clearly defined indication for the biopsy, and the risks to the patient should not outweigh the potential benefits.

Patients who are about to undergo a percutaneous liver biopsy should have had some form of imaging of the liver within the preceding weeks. This will allow the detection of abnormal anatomy in the area of the proposed biopsy.

The patient's platelet count and PT should be checked according to local hospital standards before the date of liver biopsy. Local guidelines and thresholds for hemostatic parameters should be used as they are in everyday clinical practice. Usually a platelet count >80,000/mm^3, a PT >60% or longer by no more than 4 seconds over the control, and a normal bleeding time are acceptable for performing percutaneous liver biopsy in a patient that has stopped taking any antiaggregant therapy for >5 days. If these conditions are not all respected, a safer option would be to perform the liver biopsy by transjugular route, when available.

Sedation is recommended to be given for percutaneous liver biopsy, and should be given with caution in liver disease.

The recommended biopsy procedure to be applied is:

- Needle core biopsy
- Biopsy obtained with a 16 or lower gage needle
- A tissue core ≥2 cm long (≥10 portal tracts) represents optimal biopsy length
- Preferably obtain biopsy from the right lobe. If left lobe biopsy is used for inclusion, a left lobe biopsy should be used for future biopsies.

Post-biopsy observation: It is recommended that the patient should remain in hospital at least for 6 hours after the procedure.

The biopsies will be sent to the central laboratory and then to a central reader who will read the biopsies to determine the eligibility to the study according the fibrosis stage and consistency with NASH diagnosis. Biopsy slides will be blinded for patient and visit identification prior to central reading.

6.1.1.2. Liver biopsy reading for NAS and NASH CRN fibrosis score

Histological changes from baseline to Week 72 and any follow-up biopsy will be evaluated. Liver biopsy samples will be sent to the central pathology laboratory (Hôpital Beaujon, 100 Boulevard du Général Leclerc, 92110 Clichy – France) where they will be read and scored. Scores for total NAS, steatosis, ballooning, lobular inflammation, or portal inflammation, as well as fibrosis scores (both by NASH CRN scoring system, and NAFLD Ishak scoring system) and fibrosis area by morphometry will be evaluated.

6.1.2. Biological assessments

All blood samples for efficacy and/or for safety assessment (as described in Table 2) will be returned and centralized by the central laboratory (BARC: Ghent – Belgium, New York – USA, Sydney – Australia, or Johannesburg – South Africa) and specific analyses will be performed by another laboratory (GENFIT-Loos, France).

A laboratory manual will be provided to each trial site.

The manual will outline the collection process and shipping requirements for the specific central laboratory. Blood sampling will be performed by trained personnel at each site. Blood samples will be processed and shipped as outlined in the laboratory manual. Refer to the laboratory manual for exact amounts of blood required for each test.

For all visits, laboratory results will be available at sites approximately 24 hours after receipt of samples. Final results will be couriered to sites. Laboratory reports should be reviewed, signed, and dated by the Investigator as soon as they are received. The Investigator should comment upon out of range parameters and assess clinical significance.

The option to retest during the study is left to the Investigator's judgment. During Screening, retesting (to be performed at Retesting Screening visits) is limited to HbA1c, eGFR, CPK, and HCV RNA as described Section 3.11.

6.1.2.1. Laboratory assessments

Clinical laboratory evaluations (including hematology, blood chemistry, and urinalysis) will be measured at every visit as described in Table 2.

Hematology and urinalysis (dipstick) will be measured at all visits. Both blood and urine sample will be transported to the central laboratory for testing and analysis.

At Screening, the Screening Visit 1 chemistry panel will be measured.

The V1 to Vn total chemistry panel and urine analysis will be measured at all visits from V1 to EOT visits.

6.1.2.2. Urinary pregnancy tests

Urinary pregnancy tests will be supplied to each site to perform a pregnancy diagnostic at each visit during the study on WOCBP.

6.1.2.3. Serology (SB1)

Screens for a hepatitis panel and HIV antibodies will be performed at SV1:

- HIV ab I/II
- HBsAg
- HCV ab (positive HCV RNA in case HCV ab>0, to be performed at Retesting Screening Visit)

6.1.2.4. Other parameters

Liver markers, calculated fibrosis and steatosis index, safety, and inflammatory markers, as well as special glycemic and lipid parameters, will be measured at V1, V3, V5, and V7 during the First Treatment Period, at each visit during Long-term Treatment Period, and at the EOT visit. CHI3L1 will only be tested at V1, V7, and V13 (at the time of the approximate 4 year biopsy).

6.1.3. Constitution of biobank

In order to be able to test other specific parameters which could be of interest regarding the elafibranor development program or regarding diagnosis, prevention, or treatment of NASH or other related diseases, an additional amount of serum & plasma will be kept at each visit (including Screening visits) from patients who have given their consent for these additional analyses by signature of the genetic and biomarker ICF.

These samples will be used:

- To discover or validate biomarkers in NASH and related diseases.
- To investigate the role of selected single nucleotide polymorphisms in the response to treatment.

These samples will be destroyed 3 years after study results at the latest.

6.1.4. Pharmacokinetics evaluation

6.1.4.1. Description of pharmacokinetic evaluation parameters

The aim of the PK part is to perform end of the First Treatment Period PK population analyses and to assess PK among subgroups of patients.

Elafibranor and its main active metabolite GFT1007 plasma concentrations will be evaluated at 2 timepoints (2 hours and 5 hours 45 minutes post dosing) after 72 weeks repeated once a day administrations (V7).

Pharmacokinetic parameters will be determined from elafibranor and GFT1007 plasma concentrations using a model established from a compartmental analysis.

6.1.4.2. Pharmacokinetic analysis

The PK part will be conducted at ADME BIOANALYSES (75, Chemin de Sommières - 30310 Vergèze - France) in compliance with the Standard Operating Procedures in use at ADME BIOANALYSES.

Elafibranor and GFT1007 will be assayed by measuring concentrations according to an analytical method previously developed and validated by ADME BIOANALYSES (References: PKH/MOA/528).

6.1.4.3. Pharmacokinetic blood sampling timepoints

Blood sampling will be performed for elafibranor and main active metabolite GFT1007 plasma concentration measurements, at the 2 timepoints (2 hours and 5 hours 45 minutes post dosing) after 72 weeks of treatment.

6.1.4.4. Pharmacokinetic blood handling procedures

Blood samples will be collected into one 6 mL lithium heparin Vacutainer® opaque tubes (Becton Dickinson UK Ltd., Oxford) and plasma will be separated in a refrigerated centrifuge (ca. +4°C) at ca. 2500 rpm for 15 minutes and a volume of exactly 1 mL of plasma will be dispensed in a polypropylene opaque tube for the aliquot 1 and 1.5 mL of plasma for the aliquot 2. The plasma samples will be stored at –80°C/-112°F at the site facilities.

Thereafter, the plasma samples will be transported, in dry ice, first to the central laboratory (as for all the other blood samples) where they will be stored at –80 ± 10°C (-112 ± 50°F) until shipped to ADME BIOANALYSE to be submitted to analysis.

6.2. OTHER SAFETY ASSESSMENTS AND ONGOING SAFETY MONITORING

6.2.1. Physical examination

A physical examination will be performed and weight measured at each visit (with the exception of the potential SV2). Height will be measured at SV1 only.

Weight is measured in patient in underwear and with an empty bladder. Scale for weight must be the same for a given patient throughout the visits.

6.2.2. Vital signs

Blood pressure (mmHg) and pulse rate (beats per minute) will be measured at each visit (with the exception of the potential SV2 visit) according to the "Recommendations for Blood Pressure Measurement in Humans and Experimental Animals" published in an American Heart Association scientific statement.

6.2.2.1. Important points for clinical blood pressure measurement:

- The patient should be seated comfortably with the back supported and the upper arm bare without constrictive clothing. The legs should not be crossed.
- The arm should be supported at heart level, and the bladder of the cuff should encircle at least 80% of the arm circumference.
- When using a mercury sphygmomanometer, the mercury should be deflated at 2 to 3 mm/s, and the first and last audible sounds should be taken as systolic and diastolic pressure. The column should be read to the nearest 2 mmHg.
- Neither the patient nor the observer should talk during the measurement.

Systolic BP and diastolic BP will be measured after 5 minutes rest in the seating position with a standard mercury sphygmomanometer or a validated sphygmomanometer. Validated manometer has to be the same for a given patient throughout the visits.

6.2.3. Electrocardiogram

A standard 12-lead ECG will be obtained at V1, V4, and V7 in the First Treatment Period, every 48 weeks in the Long-term Treatment Period starting at V9, and at the EOT visit.

Electrocardiograms will be recorded using 12-lead ECG recorders following after 10 minutes rest in the supine position. A minimum of 3 cycles will be recorded per lead.

The ECGs will be analyzed by the Investigator. Any potential clinical significance of ECG changes will be determined by the Investigator with relation to the patient's medical history, physical examination, and concomitant medications and recorded in the eCRF.

6.2.4. FibroScan

A FibroScan exam will be performed at V1 and V7 in the First Treatment Period, and at each visit in the Long-term Treatment Period.

For models not allowing the capture of results, a FibroScan measurement report will be provided to the sites to register the data obtained.

In case of abnormal result or sudden increase, a repeated measurement will be required 4 weeks later (to be performed at an unscheduled visit).

Recommended values for different stage of fibrosis are described in Table 3.

Table 3: Recommended values for fibrosis staging

	F0-F1(kPa)	F2(kPa)	F3(kPa)	F4(kPa)
NAFLD/NASH	**≤7.0**	**≥7.5**	**≤10**	**≥14.0**

Abbreviations: kPa = kilopascals; NAFLD = nonalcoholic fatty liver disease; NASH = nonalcoholic steatohepatitis

If at baseline, the measurement gives an abnormal value (i.e. ≥14 kPa) but without being associated with confirmed histological cirrhosis, a FibroScan measurement will be continued as planned in the protocol but will not be used for the detection of cirrhosis.

6.2.5. Quality of life questionnaire

A standardized and validated questionnaire for quality of life (SF-36) will be completed by patients at V1, V3, V5, and V7 in the First Treatment Period, and V8, V9, V11, and 48 weekly thereafter in the Long-term Treatment Period until, and including the EOT visit.

6.3. IMPORTANT SPECIFIC BIOLOGICAL CONSIDERATIONS AND PATIENT DISCONTINUATION RULES

6.3.1. Creatine phosphokinase

If at any visit during the treatment periods, a patient experiences diffuse myalgia, muscle tenderness, and/or marked increase in muscle CPK values comprised between 3 x and 5 x ULN, an additional visit and test within 3 to 7 days must be performed. If, during that visit, the patient still experiences diffuse myalgia, muscle tenderness and/or marked increase in muscle CPK values between 3 x and 5 x ULN, myopathy must be considered and the patient must be discontinued from study treatment immediately and followed up as described in Section 5.2.2.

If at any visit during the treatment periods, a patient experiences marked increase in muscle CPK values >5 x ULN, the patient must be discontinued from study treatment immediately and followed up as described in Section 5.2.2.

6.3.2. Liver function monitoring

All liver decompensation events included in the composite efficacy endpoint (Section 1.9.2) will be adjudicated by the Clinical Events Committee (CEC; see Section 6.5), as well as all DILI events (see Section 6.5).

For DILI adjudication, assessment may be performed using as baseline value the average obtained from measurements at the SV1 and V1 visits (described in the CEC manual).

6.3.2.1. Monitoring of patients with normal baseline aminotransferase values

Liver function monitoring requirements for patients with normal baseline aminotransferase (AT) values at V1 who at any visit from V2 onwards during the treatment periods exhibit:

- Increase in AT to <3 x ULN: no additional action required, schedule next visit as per assessment schedule
- Increase in AT to >3 x ULN but <5 ULN: retest after 48 to 72 hours
  If during the following retest:
  - AT remains >3 x ULN but <5 x ULN: continue the drug with close serial monitoring (once a week)
  - AT increases to >5 x ULN: permanently discontinue patient from study drug and schedule EOT Visit (see Section 3.9 and Section 5.2.2).
- Increase in AT >5 x ULN: retest after 48 to 72 hours
  If during the following retest:
  - AT remains >5 x ULN: permanently discontinue patient from study drug and schedule EOT Visit (see Section 3.9 and Section 5.2.2)
  - AT reduces to <5 x ULN: continue the drug with close serial monitoring (once a week).

6.3.2.2. Monitoring of patients with increased baseline AT values

Liver function monitoring requirements for patients with increased AT baseline values at V1 who at any visit post V1 onwards during the treatment periods exhibit:

- Increase in AT to <3 x baseline value: no additional action required, schedule next visit as per assessment schedule
- Increase in AT to >3 x baseline value but less than 10 x ULN: retest after 48 to 72 hours
  - AT remains >3 x baseline value but < 10 x ULN: continue the drug with close serial monitoring (once a week)
  - AT increases > 5 x baseline value or >10 x ULN: permanently discontinue patient from study drug and schedule EOT Visit (see Section 3.9 and Section 5.2.2).

6.3.2.3. Monitoring of all patients

Patients will permanently discontinue from study drug (see Section 3.9 and Section 5.2.2) if at any visit during the treatment periods they exhibit any of the following:

- Increase in AT (>3 x ULN or baseline value) AND increase in total bilirubin > 2 ULN
- Increase in AT (>3 X ULN or baseline value) AND increase in INR>1.5

- Increase in AT (>3 X ULN or baseline value) AND fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).

6.3.3. Threshold for diagnostic of cirrhosis

A FibroScan and serum markers assessments will be performed every 24 weeks at each visitin the Long-term Treatment Period.

In case of FibroScan ≥14 kPa, the examination will be repeated 4 weeks later (at an unscheduled visit). A liver biopsy may be considered in order to confirm the diagnosis of cirrhosis, if the repeat FibroScan value is confirmed ≥14 kPa, and associated with a platelet count <150 000/mm^3 and at least 1 elevated serum marker of fibrosis indicative of cirrhosis (NAFLD fibrosis >0.676 score or FIB-4 >2.67). In some instances, a fibroscopy may be required before any histological confirmation. In the case of detection of variceal rupture at fibroscopy or a any cirrhosis related event, such as MELD ≥15, hepatic encephalopathy, or ascites, then the liver biopsy will not be required for diagnosis of cirrhosis, but the diagnosed event will have to be adjudicated by the CEC.

If cirrhosis or any event listed in the long-term composite endpoint is diagnosed, the patient will discontinue the study drug and the study and will be followed up as described in Section 5.2.2 and Section 5.2.3.

6.4. SAFETY DATA REVIEW

An independent DSMB will be established in order to review the progress of the study and to perform a safety data review on a regular basis during the trial to protect patient welfare and preserve study integrity.

The DSMB will consist of at least 4 experienced physicians (1 each of endocrinologist, cardiologist, hepatologist, and nephrologist) and 1 statistician, all of whom will be independent of the participants in the study. A DSMB Charter will define the role, responsibilities, rules, and tasks of the DSMB.

6.5. CLINICAL EVENT COMMITTEE

The CEC will specifically assess and adjudicate all disease progression events included in the primary composite efficacy long-term endpoint (Section 1.9.2, except for histological cirrhosis), all DILI events, and all major cardiovascular events: i.e. cardiovascular death, nonfatal myocardial, infarction and stroke events as defined in the CEC manual. The CEC assessment and adjudication will occur in a blinded, consistent, and unbiased manner throughout the course of a study to determine whether the endpoints meet the protocol-specified criteria.

The CEC will comprise 2 hepatologists, and 1 cardiologist, all of whom will be independent of the participants in the study.

6.6. GUIDANCE FOR INVESTIGATORS

The safety and tolerability of GFT505 were confirmed in Phase I and Phase II studies.

A Phase I program to assess the safety and tolerability as well as the PK profile of elafibranor has been conducted through 12 clinical trials, 1 of which is still ongoing. A total of 608 volunteers were randomized in these studies performed in Phase I centers, including 536 healthy lean subjects, 60 overweight or obese subjects, and 12 patients with type 2 diabetes.

A Phase II program was initiated to assess the safety and efficacy profile of elafibranor in patients suffering from cardiometabolic disorders. To date, 5 Phase IIa pilot trials have been completed in which 297 patients were randomized. A Phase IIb trial has recently been completed, and evaluated the efficacy and safety of elafibranor 80 mg and 120 mg on steatohepatitis in 274 patients with NASH.

Of the 65 SAEs that have been reported cumulatively in the clinical development program, 44 occurred with elafibranor, 13 with placebo, and 8 prior to administration of study medication.

Of the 44 SAEs that occurred with elafibranor, only 9 were considered as having a reasonable possibility of relationship to elafibranor by the Investigators (serious adverse reaction). They consisted of:

- Atrial fibrillation in a patient with history of arterial hypertension and suspected chronic coronary disease with elafibranor 80 mg
- Acute cholecystitis & acute pancreatitis that occurred in a patient on the second day of drug administration with elafibranor 80 mg
- Spontaneous abortion in a pregnant patient treated for 6 months with elafibranor 80 mg
- Ataxia, tremor and fasciculations in a patient treated for 51 weeks with elafibranor 80 mg
- Acute pancreatitis that occurred after 7 weeks of treatment in a patient treated with elafibranor 120 mg
- Parkinson's disease in a patient treated for 12 months with elafibranor 120 mg, aged 76 years, so in the risk group for Parkinson's disease, and with a family history of Parkinson's disease.

For 3 of the SAEs (atrial fibrillation, acute cholecysto-pancreatitis, and Parkinson's disease) after later investigations, and given the medical history of the patients or the time of occurrence of the event, a relationship to elafibranor was deemed excluded by the Sponsor.

All adverse reactions (AEs reported by Investigators as possibly related or related to study drug) reported in more than 1% of patients treated with elafibranor in clinical studies with repeated doses of at least 80 mg elafibranor per day are summarized in Table 4.

Table 4: Common non-serious adverse reactions (>1% of patients treated with GFT505) by system organ class reported in completed elafibranor clinical studies with repeated administration of elafibranor (at least 14 days) from 80 mg/d up to 300 mg/d (maximum tolerated dose)

System Organ Class	Adverse Reaction	Severity	Frequency
Gastrointestinal disorders	Nausea	Mild to severe	4.4%
	Diarrhea	Mild to moderate	3.1%
	Vomiting	Mild to moderate	1.7%
General disorders and administration site conditions	Fatigue	Mild to moderate	2.0%
	Asthenia	Mild to moderate	1.1%
Musculoskeletal and connective tissue disorders	Myalgia	Mild to severe	3.1%
Investigations	Hepatic enzymes increased (mainly transaminases)	Mild to severe	1.8%
	Blood creatine phosphokinase increased	Mild to moderate	1.1%
Metabolism & nutrition disorders	Decrease appetite	Mild to severe	1.7%
Renal and urinary disorders	Renal failure/impairment	Mild to moderate	1.3%
Skin and subcutaneous tissue disorders	Rash	Mild to moderate	1.3%
Vascular disorders	Hot flush	Mild to moderate	1.3%

Among the non-serious adverse reactions, the most frequent were gastro-intestinal disorders and general disorders. The first ones consisted mostly of nausea, diarrhea, and vomiting. For general disorders, the main symptoms were fatigue or asthenia. Myalgia was also frequently reported. These are considered common and expected.

Other non-serious adverse reactions reported in more than 1% of patients concerned changes in biological parameters such as liver enzymes increase (mainly transaminases), CPK elevation, or increase of creatinine (reported by investigators as renal failure and/or impairment due to the calculation of creatinine clearance by MDRD based on creatinine). Decrease of appetite, rash and hot flush were also reported in more than 1% of patients but remain limited.

Regarding specific monitoring, although no signal for increase in CPK has been observed in the clinical trials, given the known effects of PPARalpha agonists on the increase of CPK enzyme, this parameter is monitored in clinical trials. For this reason, it is recommended that investigators review these lab results in the course of clinical trials.

Other known effects of PPARalpha agonists include the increase of creatinine, which was observed in our phase IIa and IIb trials, in a range of 5-10%. This increase was reversible at end of treatment. This should also be monitored in clinical trials.

Liver enzymes will also be monitored in clinical trials, with specific attention paid to DILI.

Based on the findings of non-clinical reproductive and developmental toxicity studies performed to date, and in the absence of human pregnancy data, GFT505 may be classed in the "Possible human teratogenicity/fetotoxicity in early pregnancy" risk category according to the Clinical Trial Facilitation Group (CTFG) document *Recommendations related to contraception and pregnancy testing in clinical trials* (September 2014).

As such, all clinical trials with GFT505 including women of childbearing potential request a negative pregnancy test before randomization, with effective contraceptive measures throughout the sudy. It is recommended to maintain the contraception up to 1 month after end of treatment. Pregnancy tests should be repeated as stated in each study protocol. In the absence of a clinical pharmacokinetic interaction study between GFT505 and contraceptive steroids, the exclusive use of hormonal contraceptive methods during clinical trials should be avoided, and they should be accompanied by barrier methods.

Conclusion

Based on the cumulative experience gathered to date, gastro-intestinal disorders such as nausea, diarrhea, and vomiting, asthenia or fatigue, myalgia are considered common and expected adverse reactions reasonably associated with GFT505. Most of them are of mild to moderate intensity. As previously, laboratory increases of serum creatinine or CPK should be monitored throughout clinical trials as this has been observed in phase 2 trials, and is a known PPARalpha agonist effect. Elevation of transaminases will be monitored as well as drug-induced liver injury. In the absence of human pregnancy data, double contraception should be maintained for women of childbearing potential participating in clinical trials with GFT505 treatment, up to 1 month after end of study treatment.

7. TREATMENTS

7.1. DESCRIPTION OF STUDY MEDICATIONS

Elafibranor (Propanoic acid, 2-[2,6-dimethyl-4-[3-[4-(methylthio)phenyl]-3-oxo-1(E)-propenyl] phenoxy]-2-methylpropanoic acid) will be supplied as 120 mg white to off-white round coated tablets with no printed inscription. The tablet contains elafibranor and inactive ingredients [redacted]

Placebo to match elafibranor 120 mg will be provided as a white to off-white round coated tablet with no printed inscription.

Standard diet and exercise recommendations (see Section 5.1.1 and APPENDIX II: Adequate diet and lifestyle recommendations) will be given at the beginning of each patient's participation and will be maintained throughout the study.

For additional information see Investigator's Brochure.

7.2. PACKAGING AND LABELING

7.2.1. Packaging

Elafibranor/placebo:

The primary packaging is composed of opaque polyamide/aluminum/PVC complex and aluminum foil blisters. This has been shown to be a suitable primary packaging for tablets.

Blisters, containing 8 tablets each, will be packed in child proof wallets.

Each childproof wallet will contain 4 blisters. Three wallets will be packaged inside a carton.

7.2.2. Labeling

All labels for study drugs meet all applicable requirements of the US Food and Drug Administration (FDA) and the EU annex 13 of Good Manufacturing Practices: Manufacture of Investigational Medicinal Products (July 2003) and /or other local regulations, as applicable.

Distribution of study drug will be performed according to the Good Distribution Practices.

Product cartons will be labeled with the protocol number, Sponsor's name and address, description of contents, storage conditions, expiry date, dosage instructions, and any other applicable items required by national and regional guidelines/regulations. The label will contain the statements "For clinical trial use only" or other similar/appropriate statements as well as the following instructions "Please return empty

packaging and unused products to your doctor at your next visit." Details of carton and wallet labels are detailed in APPENDIX V: PRODUCT CARTON AND WALLET LABELING.

7.2.3. Dosage and administration of Elafibranor and placebo

Patients will be informed to take one tablet per day of elafibranor 120 mg or placebo orally before breakfast with a glass of water each morning.

7.2.4. Prior and concomitant medications

All concomitant medications will be recorded in the source documents and eCRF. This includes concomitant medications taken within 30 days prior to Screening and any taken during the study.

Upon screening of the first patient, the system will immediately forward the information to the Drug Distribution Center which will be responsible to send one of several blocks of treatment packages (containing 96 tablets to last approximately 3 months) allocated to the site. The pharmacy will acknowledge receipt of the study drug in the IXRS.

An e-mail, confirming that the patient has been screened, will be sent to the Investigator, [redacted] and to the Sponsor.

After having received the liver biopsy results as well as the SV1 laboratory results (SB1) (or when applicable, results of any retesting performed) , and if the patient fulfills all criteria to enter the treatment period, the Investigator will register the patient in the IXRS to randomize him/her.

The IXRS will check if the Investigator is authorized to use the system (identification number and access code) and will ask some questions to check the patient eligibility. The IXRS will then allocate the patient to a treatment group (elafibranor 120 mg or placebo) through a patient number (with 7 digits), as described in Section 3.2.

A specific IXRS procedure manual will be provided to the pharmacy.

The randomization list will be generated by the IXRS partner and will be kept in blinding condition to the study participants until the Blind-Review Meeting and the Sponsor authorization to unblind the trial.

7.3. STORAGE CONDITIONS

Elafibranor and placebo should be stored between +15°C and +25°C (59°F and 77°F). Storage conditions are specified on the label.

7.4. DISPENSING OF TREATMENT

Each site will have a resupply strategy within the IXRS (as defined in the Drug Shipment Details document) to determine the supply of study drugs sent to each site. Initial site shipments will be shipped at a static

value defined in the supply strategy. Following randomization of a patient IXRS will project for the amount of study drug required for future visits and ensure the study drug is at site for the visits occurring. The IXRS will continue to project study drug requirements per patient until an event occurs which stops the projections for that patient.

The Investigator will register the patient's visit in the IXRS who will allocate to the patient a treatment package for approximately 3 months (96 tablets) in the First Treatment Period and for approximately 6 months (192 tablets) in the Long-term Treatment Period. An e-mail, confirming the registration, will be sent to the Investigator and to the Sponsor.

The treatment package will include a carton with 3 wallets of 4 blisters for the First Treatment Period and 2 cartons with 3 wallets of 4 blisters in the Long-term Treatment Period.

Each randomized patient will be given, from V1 and at every following visit, the study medication containing the adequate number of wallets to cover the drug administration for the period between visits. The time between visits will be 12 weeks ± 1 week (to a maximum of 96 days) during the First Treatment Period and 24 weeks ± 2 weeks (to a maximum of 192 days) between visits in the Long-term Treatment Period, which correspond to the number of tablets provided to the patient at each visit.

7.5. TREATMENT REPLACEMENT

A specific IXRS procedure manual will be provided to the Investigator and will detail the procedure in case of need of treatment replacement.

7.6. PROCEDURE FOR BLINDING

The Investigator, patient, and study personnel will be blinded to the treatment.

Identification numbers will be assigned to a patient at the Screening Visit. The number will also be reported in the eCRF. Upon completion of the Screening visit(s), eligible patients will be randomly assigned to active treatment (elafibranor 120 mg) or placebo at the first visit of the First Treatment Period (V1).

7.7. PROCEDURE FOR UNBLINDING

The randomization code may be broken by the Investigator when urgent action is required for the clinical management of the patient. For each patient, the list of treatment numbers allocated to the patient will be stored in the IXRS. The Investigator will be able to unblind any treatment box that was dispensed to the patient by connecting the IXRS (**24-hour & 7-day access**) and entering their identification number and access code. A back-up phone Interactive Response Technology (IRT) module will also be available should the site be unable to access the internet. The IXRS will verify the authorization to unblind the entered treatment box and the screen will then display the treatment group, when completed, a blinded confirmatory e-mail will be sent to the Investigator and the Sponsor.

The reason for unblinding should be clearly and fully documented by the Investigator.

7.8. STUDY DRUG COMPLIANCE

From V2 and at every following visit while the patient is being treated with study drug, the patient will be directed to bring back all used and unused boxes and blisters. Compliance will be checked by the Investigator during those visits and registered in the eCRF.

If treatment is interrupt, whatever the cause, duration and reason of the interruption should be documented.

7.9. TREATMENT ACCOUNTABILITY, RETRIEVAL AND DESTRUCTION.

The Investigator or pharmacist will sign a receipt for each study treatment on the day of receipt. A drug accountability record should be maintained by the person responsible for dispensing the trial medication to the patient.

All partially used or unused treatments will be inventoried by the monitor during and at the conclusion of the study.

On Sponsor request, the Drug Distribution Center will organize the retrieval of all treatments (used or unused) and will proceed to their destruction only after the Sponsor provides written authorization.

If the site has an appropriate Standard Operating Procedure (SOP) for drug destruction, the site may destroy used and unused study drugs in accordance with the site SOP and always after the drug accountability has been performed by the monitor.

If drug is destroyed in the site, the Investigator must maintain accurate records for blisters destroyed recording:

- Blister identification
- Quantity destroyed
- Method of destruction
- Person who disposed the drug.

7.10. OTHER MEDICATION

7.10.1. Handling of concomitant medication

In a general manner, patients should be discouraged from starting any new medication without consulting the Investigator unless the new medication is required for emergency purpose. **In the same way, any qualitative or quantitative change in concomitant therapy should be avoided, when possible**.

In the event that it becomes necessary during the study, this should be recorded by the Investigator in the eCRF and information should be communicated to the Medical Monitor in order to evaluate the risk of DDIs. This includes drugs used on a chronic as well as on an "as needed" basis.

7.10.2. Non-permitted medication

The following medications are not allowed within the timeframe given in APPENDIX III: Permitted/Non-permitted medication):

- Glitazones (pioglitazone & rosiglitazone)
- Fibrates
- Corticosteroids (parenteral & oral chronic administration only)
- Amiodarone
- Tamoxifen
- Methotrexate
- Indomethacin.

The following medication is not allowed to be initiated during the treatment periods of the study (see APPENDIX III: Permitted/Non-permitted medication):

- GLP-1 agonist.

If it is identified after Randomization that these non-permitted drugs have been administered to a patient within the excluded timeframes, the patient will be permanently discontinued from the study drug (see Section 5.2.2).

7.10.3. Permitted medication under condition (see **APPENDIX III: Permitted/Non-permitted medication**)

- The following medications are permitted under the condition of steady dosage prior to Screening:
  - statins and ezetimibe provided the dosage is kept stable for at least 2 months prior to Screening

- The following medications are permitted under the condition of stable dose from at least 6 months prior to diagnostic liver biopsy:
  - vitamin E >400 IU/day
  - PUFAs >2 g/day
  - ursodeoxycholic acid
  - GLP-1 agonist.

Importantly, no initiation of GLP-1 agonists will be allowed during the treatment periods of the study. Should the Investigator decide to initiate this drug, it would lead to permanent discontinuation of the patient from the study drug (see Section 5.2.2).

- The following medications are permitted under the condition of no qualitative change (i.e., implementation of a new antidiabetic drug) in the 6 months prior to diagnostic liver biopsy:
  - insulin
  - sulfamides
  - metformin
  - gliptins
  - SGLT2-inhibitors.

Patients on sulfamides and insulin are recommended to self-monitor blood glucose.

7.10.4. Permitted medication

Any medications other than those listed above are permitted. However, the dosage of a current medication for a chronic disease should remain unchanged as far as possible in order to reduce the risk of unknown DDIs.

In the event that additional concomitant therapy becomes necessary during the study, this should be recorded by the Investigator in the eCRF. This includes drugs used on a chronic as well as on an "as-needed" basis. Patients should be discouraged from starting any new medication without consulting the Investigator unless the new medication is required for emergency purpose.

8. ADVERSE EVENT AND TOXICITY MANAGEMENT

8.1. DEFINITIONS

8.1.1. Adverse event

Any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical (investigational) product and which does not necessarily have to have a causal relationship with this treatment will be considered as an AE. The term AE is synonymous with the term "adverse experience" as used by the FDA.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding or physiological observation, for example), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal product.

Examples of AE include (but are not limited to): abnormal test findings; clinically significant symptoms and signs; changes in physical examination findings; hypersensitivity; progression/worsening of pre-existing condition or underlying disease; recurrence of a pre-existing condition; lack of effect, complication, and termination of pregnancy.

Additionally, they may include the signs or symptoms resulting from: drug overdose, drug withdrawal, drug abuse, drug misuse, drug interactions, drug dependency, extravasation, exposure in utero.

The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

- Test result is associated with accompanying symptoms
- Test result requires additional diagnostic testing or medical/surgical intervention
- Test result leads to a change in trial dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy
- Test result is considered to be an AE by the Investigator or Sponsor.

Repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

An AE does not include the following:

- Medical or surgical procedures performed; the condition that leads to the procedure may be an AE if applicable
- Pre-existing disease, condition or laboratory abnormalities present or detected before the Screening Visit that do not worsen
- Overdose without clinical sequelae

- Any medical condition, or clinically significant laboratory abnormality with an onset before the consent form is signed. Such as medical condition is considered to be pre-existing and should be documented on the medical history of the eCRF
- Uncomplicated pregnancy
- An induced elective abortion to terminate a pregnancy without medical reason
- Events that are identified as efficacy endpoints for the long-term evaluation (described in Section 1.9.2) should not be reported as AE. For more details on endpoint reporting, please refer to the CEC Manual.

The questions concerning whether the condition existed before the start of the active phase of the study and whether it has increased in severity and/or frequency will be used to determine whether an event is a treatment-emergent AE. An AE is considered to be treatment emergent if (1) it is not present when the active phase of the study begins and is not a chronic condition that is part of the patient's medical history, or (2) it is present at the start of the active phase of the study or as part of the patient's medical history, but the severity or frequency increases during the active phase. The active phase of the study begins at the time of the first dose of the study drug. The active phase of the study ends at the follow-up visit.

8.1.2. Serious adverse events

A SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (see Section 8.1.2.1)
- Requires inpatient hospitalization or prolongation of existing hospitalization (see Section 8.1.2.2)
- Results in persistent or significant disability/incapacity (see Section 8.1.2.3)
- Is a congenital anomaly/birth defect (including fetal malformations associated with spontaneous abortions or elective abortions)
- Is another medically important condition (see Section 8.1.2.4).

In addition, any illnesses reported before starting active treatment or AE meeting the criteria of seriousness (as defined above) and considered to be possibly related (according to the Investigator) to any study-specific procedure (e.g. wash-out period, laboratory testing procedure) must be reported as an SAE.

8.1.2.1. Life-threatening adverse events

A life-threatening AE in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

8.1.2.2. *Inpatient or prolonged hospitalization*

An inpatient hospitalization or prolongation of a hospitalization means that the patient stays overnight in the hospital. Pre-planned hospital stays or hospital stays for nonmedical social reasons will not be considered as hospitalization, for example:

- Hospitalization or prolongation of hospitalization is needed for a procedure required by the protocol. Day or night survey visits for biopsy or surgery required by the protocol are not considered serious.
- Hospitalization or prolongation of hospitalization is part of a routine procedure followed by the study center (e.g., stent removal after surgery). This should be recorded in the study file.
- Hospitalization for survey visits or annual physicals fall in the same category.
- Hospitalization planned before the start of the study for a pre-existing condition that has not worsened does not constitute an SAE (e.g., elective hospitalization for a total knee replacement due to a pre-existing condition of osteoarthritis of the knee that has not worsened during the study).

8.1.2.3. Significant or incapacitating disability

Only a persistent or significant or incapacitating disability is intended. This item refers to a substantial disruption of a person's ability to conduct normal life functions. Thus, disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma.

8.1.2.4. Medically important conditions

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

Examples of such events are:

- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias or convulsions that do not result in hospitalization
- Development of drug dependency or drug abuse.

8.1.3. Clarification on serious adverse events:

- As an outcome event, progression to cirrhosis should not be included as AE.
- Death is an outcome of an AE, not an AE in itself.

- An SAE may occur even if the patient was not being treated with the investigational medicinal product at the occurrence of the event.
- Life-threatening means that patient is at immediate risk of death. This does not include an event that might have led to death if it had occurred with greater severity.
- Complications that occur during hospitalizations are AEs. If a complication prolongs the hospitalization, it is a SAE.
- Patient hospitalization means that the patient stays overnight in the hospital. Pre-planned hospital stays or hospital stays for nonmedical social reasons will not be considered as hospitalization.
- A procedure for protocol/disease-related investigations (e.g., biopsy) should not be reported as SAE. Hospitalization or prolonged hospitalization for a complication of such procedures should be reported as SAE.

8.1.4. Adverse drug reaction

An adverse drug reaction (ADR) is defined as a response to a medicinal product which is noxious and unintended and that is considered casually related to an investigational medicinal product. A serious ADR (SADR) is an ADR which meets the seriousness criteria.

8.1.5. Unexpected adverse event

Expectedness is assessed by the Sponsor. An unexpected AE is defined as an event that has a nature of severity or specificity that is not consistent with the applicable Investigator Brochure or that is symptomatically and pathophysiological related to a known toxicity but differs because of a greater severity or specificity.

"Unexpected" refers to an ADR that has not been previously observed and reported rather than an event that has not been anticipated based on the properties of the drug.

8.2. ASSESSMENTS

The Investigator will establish whether or not any AE have occurred at each visit from the date of consent. The patient will be questioned in a general manner to determine specific symptoms without offering the patient any suggestion.

8.2.1. Intensity assessment

The intensity of the AE will be graded as follows:

- **Mild**: Awareness of signs or symptoms, but easily tolerated and are of minor irritant type causing no loss of time from normal activities. Symptoms do not require therapy or a medical evaluation; signs and symptoms are transient.

- **Moderate**: Events introduce a low level of inconvenience or concern to the participant and may interfere with daily activities, but are usually improved by simple therapeutic measures; moderate experiences may cause some interference with functioning.
- **Severe**: Events interrupt the participant's normal daily activities and generally require systemic drug therapy or other treatment; they are usually incapacitating.

8.2.2. Relation to the study treatment

The Investigator will make a clinical and scientific judgment regarding whether or not the AE was related to study treatment. The Investigator will evaluate any changes in laboratory values, make a determination as to whether or not the change is clinically important, and whether or not the changes were related to study drug. However, even if the Investigator feels there is no relationship to the study drug, the AE or clinically significant laboratory abnormality must be recorded in the eCRF.

The Investigator will record the relation to the study treatment according to the following causality terms:

- **Related:** the AE follows a reasonable temporal sequence from the time of drug administration and it cannot be explained by the patient's clinical state or the study procedures/conditions. The AE abates upon discontinuation of the study drug and reappears when the study drug is introduced.
- **Possibly related:** the AE follows a reasonable temporal sequence from the time of drug administration, but could have been produced by the patient's clinical state or the study procedures/conditions.
- **Unlikely related:** the temporal association between the AE and the study drug is such that the study drug is not likely to have any reasonable association with the AE. The relationship is not likely because of other plausible explanations.
- **Not related:** the AE must definitely be caused by the patient's clinical state or the study procedure/conditions. A reasonable explanation must be given, e.g., no investigational product taken, preplanned elective medical intervention, or incompatible temporal relationship.
- **Not assessable**: the report suggesting an adverse reaction cannot be judged because information is insufficient or contradictory and data cannot be supplemented or verified.

8.2.3. Action taken and outcome

The Investigator will record the action taken with drug and outcome of the event for each AE according to the following:

<u>Action taken with investigational drug</u>

- Drug permanently withdrawn – in case a patient is permanently withdrawn from the study drug
- Drug temporarily withdrawn – in case the study drug is temporarily withdrawn
- Dose not changed – in case no action is taken regarding the study drug

- Unknown
- Not applicable – an AE started before initiation of treatment with study drug, the treatment had been completed prior to reaction/event, or the patient has died.

Outcome

- Recovered/resolved
- Recovering/resolving
- Not recovered/not resolved
- Recovered/resolved with sequelae
- Fatal
- Unknown.

Note: In case of irreversible congenital anomalies the choice not recovered/not resolved should be used. "Fatal" should be used when death is possibly related to the reaction/event.

8.3. REPORTING

8.3.1. Reporting an adverse event

All AEs regardless of seriousness or relationship to study drug, including those occurring during the Screening Period, are to be recorded on the corresponding page(s) of the eCRF and in the patient's medical record from the ICF signature until the final follow-up visit. Whenever possible, symptoms should be grouped as a single syndrome or diagnosis. The Investigator should specify the date of onset, maximal intensity, action taken with respect to study drug, corrective therapy given, outcome, and his/her opinion as to whether there is a reasonable possibility that the AE was caused by the study drug.

Adverse event reporting begins from signature of the patient ICF at the first Screening visit and ends at the last study visit.

8.3.2. Reporting a serious adverse event

Serious AE reporting begins from signature of the patient ICF and ends at the last study visit.

Any SAE that is brought to the attention of the Investigator at any time after the reporting period and which is considered by him/her to be caused by the study drug within a reasonable possibility, should be reported

Events that are identified as potential efficacy endpoints for long-term evaluation will NOT be reported as SAEs unless it is determined by the adjudication committee that the event does not meet the predefined criteria for an endpoint. Events that are identified as potential efficacy endpoints for long-term evaluation that are not confirmed by adjudication will be reported as described with the start of the reporting time window being the time of negative adjudication decision.

Investigators must notify, by fax or e-mail, the Sponsor designated representative [redacted] of all SAEs **IMMEDIATELY (within 24 hours of the Investigator becoming aware of the event).**

ANY SERIOUS ADVERSE EVENTS, WHETHER OR NOT RELATED TO THE STUDY DRUG, MUST BE REPORTED IMMEDIATELY (WITHIN 24 HOURS) TO [redacted] AT THE FOLLOWING FAX NUMBERS:

FAX numbers: [redacted]

Contact Person: [redacted]

E-mail: [redacted]

All SAEs independent of the circumstances or suspected cause must be reported in ENGLISH on a SAE Form. The SAE Form should include a clearly written narrative describing signs, symptoms, and treatment of the event, diagnostic procedures, as well as any relevant laboratory data and any sequelae, in order to allow a complete medical assessment of the case and independent determination of the possible causality.

The Investigator is also required to submit follow-up SAE reports to [redacted] within 24 hours of becoming aware of additional information such as diagnosis, outcome, causality assessment, results of specific investigations, and any new significant information that has not been previously reported.

It is critical that the information provided on the initial or follow-up SAE Form matches the information recorded in the source documents and the eCRF for the same event.

Copies of additional laboratory tests, consultation reports, postmortem reports, hospital case reports, autopsy reports, and other documents should be sent when requested and applicable. All provided reports must be anonymized.

Follow-up reports relative to the patient's subsequent course must be submitted to [redacted] until the event has subsided or, in case of permanent impairment, until the condition stabilizes.

The Sponsor or its designated representative will report all the relevant safety information to the concerned Competent Authorities and to the Independent Ethics Committee(s) (IRB/IEC) concerned according to the country-specific requirements.

Investigator must fulfill his/her regulatory obligations to the Regulatory Authorities and/or to the Ethics Committee in accordance with local regulations.

Depending on local regulations in different regions and countries, the Sponsor or designated clinical research organization (CRO) may be required to expedite report to the Regulatory Authorities for:

- SAEs (including events related to study procedures)
- SADRs
- Suspected unexpected serious adverse reactions (SUSARs)

Each SAE report received from the Investigators will be evaluated by the designated CRO for pharmacovigilance who will assess the seriousness of the event. Each SAE report will be evaluated by the Sponsor and/or his designees who will assess the relationship to study procedure or study treatment and the expectedness of the event. Expectedness will be assessed using the reference safety information included in the Investigator Brochure.

Any unexpected safety issue that changes the risks benefit analysis and is likely to have an impact on the patients who have participated in it will be reported by the Sponsor as soon as possible to the Competent Authority(ies) concerned together with proposed actions.

8.3.3. Follow-up

The Investigator should take all appropriate measures to ensure the safety of the patients, notably he/she should follow up the outcome of any AE until the return to normal or until consolidation of the patient condition.

The patient must be followed up until clinical recovery is complete and laboratory results have returned to normal, or until progression has been stabilized. This may imply that follow-up will continue after the patient has left the study and that additional investigations may be requested by the Sponsor. This information should be documented in the patient's medical records.

8.4. POST STUDY REPORTING REQUIREMENTS

Any SAEs and deaths that occur within 30 days of the last dose of the study drug, regardless of causality, should also be reported.

Any SAE that is brought to the attention of the Investigator at any time after the reporting period and which is considered by him/her to be caused by the study drug within a reasonable possibility, should be reported.

8.5. CLINICAL LABORATORY ABNORMALITIES AND OTHER ABNORMAL ASSESSMENTS AS ADVERSE EVENTS OR SERIOUS ADVERSE EVENTS

Laboratory abnormalities are not necessarily recorded as AEs or SAEs. However, laboratory abnormalities that are considered clinically relevant by the Investigator must be recorded as an AE or SAE as applicable.

8.6. SPECIAL SITUATION REPORTS

Special situations reports include pregnancy reports, reports of medication error, abuse, misuse or overdose, and reports associated with product complaints.

8.6.1. Pregnancy

In case of pregnancy a communication will be sent by the Investigator to [redacted] by faxing a completed pregnancy form within 24 hours of his/her knowledge of the pregnancy.

Pregnancies of females partners of male patients exposed to study medication should also be reported to [redacted] using the corresponding pregnancy form.

Female patients must be instructed to discontinue the study drug immediately and inform the Investigator as soon as possible once they are aware of being pregnant or suspect that they are pregnant during the study or within 30 days of the last dose of the study drug.

Female patients will be requested, as part of the general ICF, to provide informed consent to allow reasonable attempts to be made to obtain information on any possible medicinal product exposure to an embryo or fetus and to follow up on the outcome of the pregnancy.

The Investigator will contact the patient at the expected time of delivery for follow-up. If the outcome of pregnancy meets the criteria for immediate classification of an SAE (e.g., spontaneous or therapeutic abortion, stillbirth, neonatal death, congenital anomaly, birth defect), the Investigator should follow the procedure for reporting SAEs as detailed in Section 8.3.2.

The pregnancy itself is not considered an AE.

8.6.2. Medication error

Medication error is defined as an unintentional error in the prescribing, dispensing, or administration of a medicinal product while in the control of the healthcare professional, patient, or consumer. All medication errors will be documented in the eCRF and, in case of any potential risk to patient safety, would be reported as appropriate (see Section 8.3).

8.6.3. Misuse

This refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the authorized product information and will be reported in the eCRF. All misuse will be documented in the eCRF and, in case of any potential risk to patient safety, would be reported as appropriate (see Section 8.3).

8.6.4. Overdose

This refers to the administration of a quantity of a medicinal product given per administration or cumulatively, which is above the maximum recommended dose according to the authorized product information (see Section 8.1.1 and Section 8.3.1). Clinical judgment should always be applied.

8.6.5. Abuse

This corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

9. STATISTICAL METHODS AND DATA ANALYSIS

This section is an overview of the key elements of the statistical analysis for this study. Further details on statistical reporting and analyses will be contained in a separate statistical analysis plan (SAP). This SAP may be revised during the study only to accommodate protocol amendments and to make changes to adapt to unexpected issues in study execution and data collection that could affect planned analyses. In all circumstances, a final SAP should be issued prior to database lock and treatment unblinding. The first approved version of the SAP should be available within 3 months of protocol submission and before the first DSMB meeting.

The main analyses will be based on patients with fibrosis stage F2 and F3. The summaries will be repeated in an exploratory manner with the inclusion of patients with fibrosis stage F1.

9.1. RANDOMIZATION AND TREATMENT ASSIGNMENT

Random allocation will be made to the 2 treatment groups (elafibranor and placebo) in a 2:1 ratio basis and stratified by the following factors:

- Type 2 diabetes (yes, no)
- Gender (male, female) (with a capping of women to 40%)
- Fibrosis stage (F1, F2, F3) (capped to 202 F1 patients).

Details on the randomization process are in Section 3.2.

9.2. ENDPOINTS

9.2.1. Surrogate endpoint - resolution of NASH

The first surrogate endpoint for this study is resolution of NASH without worsening of fibrosis after 72 weeks of treatment with elafibranor. Resolution of NASH is defined as the disappearance of ballooning (i.e., grade 0) and disappearance or persistence of minimal lobular inflammation (i.e., grade 0 or 1) with an overall pattern of injury not qualifying for steatohepatitis. Worsening of fibrosis is evaluated using NASH CRN fibrosis staging system and defined as progression of at least 1 stage. This surrogate endpoint will be formally assessed at the time of the interim analysis when approximately 50% (at least 1023) of the F2 to F3 patients complete the 72 week treatment period or discontinue early from the study (see Section 9.8.1 for details. An additional exploratory analysis of this endpoint will take place at the time of the final analysis.

9.2.2. Long-term endpoint – time to clinical event/death

To evaluate the efficacy of elafibranor on clinical outcomes described as a composite endpoint composed of death to any cause, liver cirrhosis and the full list of portal hypertension/cirrhosis related events:

- Liver transplantation
- MELD score ≥15
- HCC
- Hospitalization (as defined by a stay of 24 hours or greater) for new onset or recurrence of:
    - variceal bleed
    - hepatic encephalopathy
    - spontaneous bacterial peritonitis
    - uncontrolled ascites
    - hepatorenal syndrome
    - hepatopulmonary syndrome
    - chronic gastrointestinal blood loss due to portal hypertensive gastropathy (provided that these lead to hospitalization or transfusion).

The final analysis will be performed when 456 patients experience an event listed above. This is expected to occur approximately 72 months after the first patient is randomized.

9.2.3. Key Secondary Endpoint

The key secondary endpoint is:

- Percentage of patients with improvement of fibrosis of at least 1 stage according to NASH CRN scoring at 72 weeks.

This key secondary endpoint will be assessed at the time of the interim analysis (on approximately 50% of the patients) for the resolution of NASH without worsening of fibrosis endpoint.

9.2.4. Other Secondary Endpoints

The other secondary endpoints are:

- To assess histological changes after 72 weeks of treatment and follow-up biopsy on the following parameters:
    - percentage of patients with resolution of NASH without worsening of fibrosis (follow-up biopsy)
    - percentage of patients with improvement of fibrosis of at least 1 stage according to NASH CRN scoring
    - percentage of patients with at least 1 point improvement in histological scores (NASH CRN scoring: total NAS, steatosis, hepatic ballooning, lobular inflammation), fibrosis (NAFLD Ishak scoring system), or portal inflammation
    - percentage of patients improvement of NAS score of at least 2 points
    - percentage of patients with at least a 1 point improvement in SAF activity score

  - mean changes in NAS score, fibrosis, steatosis, hepatic ballooning, lobular inflammation, portal inflammation, SAF activity score
  - changes in area of fibrosis by morphometry
  - mean changes in fibrosis using NASH CRN and NAFLD Ishak scoring.
- To assess the following endpoints in elafibranor treated patients relative to placebo, at Week 72 and at the end of the Long-term Treatment Period:
  - cardiovascular events
  - liver-related death events
  - changes in liver enzymes and liver markers
  - changes in noninvasive markers of fibrosis and steatosis
  - changes in lipid parameters
  - variation in body weight
  - changes in insulin resistance and glucose homeostasis markers
  - changes in inflammatory markers
  - changes in cardiovascular risk profile as assessed by Framingham scores
  - changes in quality of life (SF-36 questionnaire).

- Time to first occurrence of:
  - liver cirrhosis
  - death of any cause
  - any portal hypertension or cirrhosis related events.

9.2.5. Exploratory endpoints

The exploratory endpoints are:

- To determine PK parameters of elafibranor (GFT505) and its metabolite GFT1007 after 72 weeks of treatment for PK population analyses.
- To constitute a biobank for discovery and validation of biomarkers in NASH.

Details on all endpoints will be given in the SAP.

9.3. ANALYSIS SETS

The following analysis sets will be used in this study:

- Enrolled: all patients who sign informed consent. This set will be used to summarize disposition.
- ITT: all randomized F2 and F3 patients. This set will be used to summarize efficacy. The main analysis of the primary and key secondary endpoints will be based on the ITT.
- Safety set (SS): all randomized F2 and F3 patients who receive at least 1 dose of study drug. This set will be used to summarize safety.

- Per protocol set (PPS): all F2 and F3 patients who receive at least 1 dose of study drug and do not have any important protocol deviations leading to exclusion from the PPS. Important protocol deviations will be defined in the SAP and agreed prior to database lock. . Supportive analysis of the primary and key secondary endpoints will be based on the PPS.
- PK set (PKS): All F2 and F3 patients who have taken at least 1 dose of elafibranor and have sufficient plasma concentrations to be able to derive the various PK parameters.
- Exploratory F1 cohort: All randomized F1 patients who have taken at least 1 dose of study drug.
- Full Intent-To-Treat Set (FITT): all randomized patients.
- Full Safety Set (FSS): all randomized patients who receive at least 1 dose of study drug.
- Full PK Set (FPKS): All patients who have taken at least 1 dose of elafibranor and have sufficient plasma concentrations to be able to derive the various PK parameters.

Patients in the ITT, FITT, PPS,and exploratory F1 cohorts (study population and efficacy data) will analyzed based on randomized treatment. Patients in the SS, FSS, PKS, FPKS, and exploratory F1 cohorts (safety data) will be analyzed based on actual treatment received.

9.4. ANALYSIS OF PRIMARY ENDPOINTS

9.4.1. Resolution of NASH

The null hypothesis for resolution of NASH without worsening of fibrosis is that there is no difference in response rates between the elafibranor and placebo groups. The alternative hypothesis is that there is a difference in response rates between the elafibranor and placebo groups. The null hypothesis will be tested at the two-sided 0.01 alpha level.

The number and percentage of patients with resolution of NASH without worsening of fibrosis at the end of the 72 week treatment period will be summarized by treatment group. The main analysis will be performed using a logistic regression model, with fixed terms for treatment, type 2 diabetes (yes, no), gender (male, female), fibrosis stage (F2, F3) and baseline NAS. The statistical model will be used to calculate the odds ratio (elafibranor/placebo) and 95% confidence interval. The main confirmatory analysis will be performed when approximately 50% of patients (at least 1023) have completed the 72 week treatment period or discontinued from the study. The main analysis will be based on the ITT. Supportive analysis will be based on the PPS.

Patients with missing data for resolution of NASH without worsening of fibrosis will be treated as a nonresponder for the main analysis. Additional sensitivity analysis using multiple imputations and a pattern mixture model will be performed. Further details will be provided in the SAP.

9.4.2. Long-term endpoints

The null hypothesis for time to clinical event/death is that there is no difference in the survival distributions between the elafibranor and placebo groups. The alternative hypothesis is that there is a difference in the

survival distributions between the elafibranor and placebo groups. The null hypothesis will be tested at the two-sided 0.04 alpha level.

The data will be analyzed using a Cox proportional hazards model with fixed terms for treatment, type 2 diabetes, gender, fibrosis stage, and baseline NAS. The Cox proportional hazards model will be used to calculate the hazard ratio (elafibranor/placebo) and 95% confidence interval. This will be performed when at least 456 patients experience a clinical event/death.

The time to clinical event/death will be presented graphically using a Kaplan-Meier curve. The median time to first clinical event/death and 95% confidence interval will also be presented for each treatment group.

Missing data will be censored at the last known date.

The main analysis will be based on the IIT. Supportive analysis will be based on the PPS.

9.5. OTHER STATISTICAL ANALYSIS

9.5.1. Key secondary endpoint

The number and percentage of patients with improvement of fibrosis according to NASH CRN scoring at the end of the 72 week treatment period will be summarized separately by treatment group. The data will be analyzed using a logistic regression model, with fixed terms for treatment, type 2 diabetes, gender, fibrosis stage and baseline NAS.

The analysis will be performed at the time of the interim analysis when approximately 50% of patients (at least 1023) have completed the 72 week treatment period or discontinued from the study.

The main analysis will be based on the IIT. Supportive analyses will be based on the PPS.

9.5.2. Other secondary endpoints

All other secondary endpoints will be summarized by treatment group using descriptive statistics. The main analysis will be based on the ITT.

Categorical endpoints will be analyzed using a logistic regression model in the same manner as resolution of NASH without worsening of fibrosis.

Time to event endpoints will be analyzed using the Cox proportional hazard's model in the same manner as time to clinical event/death.

Continuous endpoints will be analyzed using an Analysis of Covariance (ANCOVA) model with fixed terms for treatment, type 2 diabetes, gender, fibrosis stage, and baseline NAS. An unstructured covariance matrix will be used for this analysis. The statistical model will be used to calculate the mean treatment difference and 95% confidence interval. If the data does not meet the required assumptions for parametric tests, the

data will be analyzed using a nonparametric Wilcoxon rank sum test. The median treatment difference and 95% confidence interval will be calculated using the Hodghes-Lehmann method.

Further details will be in the SAP.

9.5.3. Subgroup analyses

Exploratory analyses of the primary and key secondary endpoints will be done for selected subgroups, including, but not limited to, the following:

- Presence of type 2 diabetes (yes, no)
- Gender (male, female)
- Fibrosis (F2, F3)
- Geographic region (North America, Europe, South America, Rest of World)
- Race (Caucasian, Hispanic, Other)
- Age (<55, ≥55 years).

Forest plots will be generated for each of these endpoints for patients in the ITT population.

9.5.4. Exploratory analyses

Additional exploratory analyses of the efficacy data will be performed on the exploratory F1 cohort.

9.6. STRATEGIES TO CONTROL TYPE I ERROR

The overall type I error for this study is two-sided α=0.05. The alpha for the primary endpoints will be split 20%/80%, with two-sided α=0.01 for resolution of NASH and two-sided α=0.04 for time to clinical event/death. The overall type I error for the primary endpoints in this study is two-sided α=0.05. The alpha for the primary endpoints will be split 20%/80%, with two-sided α=0.01 for resolution of NASH and two-sided α=0.04 for time to clinical event/death.

A hierarchical gate-keeping strategy will be used to control for multiplicity for the key secondary endpoint. If the resolution of NASH without worsening of fibrosis endpoint is statistically significant, the key secondary endpoint, improvement of fibrosis according to NASH CRN scoring, will be tested in a confirmatory manner with a two-sided α=0.5.

Statistical testing for all other secondary endpoints will be of exploratory nature.

As this is a single pivotal study that will be used for a regulatory submission, the consistency of the results for the primary and key secondary endpoints will be further explored by population and selected subgroups. In addition, different approaches will be applied for dealing with missing data.

9.7. SAMPLE SIZE CALCULATION

All sample size calculations were done in EAST 6.3.

9.7.1. Resolution of NASH

The following assumptions were made for the sample size calculation for resolution of NASH:

- α=0.01 two-sided
- Randomized patients with no response assessment at Week 72 will be counted as nonresponders
- Pooled variance
- Randomization ratio of 2:1 (elafibranor: placebo)
- 8% response in the control group
- 16.5% response in the elafibranor group

The 8% response rate in the placebo group (calculated as the mean response rate based on the Phase II FLINT study[35] [subanalysis including only patients with stage 2 and stage 3 fibrosis or stage 1 fibrosis with diabetes, obesity or ALT ≥ 60 {associated with fibrosis progression}; placebo response rate 6.5%] and the GFT505-212-7 placebo data [11% response rate for patients with any stage fibrosis {F1; F2; F3} and 7% response rate for patients with only stage 2 and 3 fibrosis]). The 16.5% response rate in the elafibranor group is based on the Phase II GFT505-212-7 elafibranor data (calculated as the mean response rate based on a 20% response rate for patients with any stage fibrosis ([F1; F2; F3] and 13% response rate for patients with only stage 2 and 3 fibrosis).

Based on these assumptions, a sample size of 1023 patients provides 90% power to show that elafibranor is superior to the placebo with respect to resolution of NASH without worsening of fibrosis.

9.7.2. Time to clinical event/death

The following assumptions were made for the sample size calculation for time to clinical event/death:

- 24 month enrollment (with an 18-month ramp up to as many as 200 patients per month)
- 72 month maximum follow-up
- α=0.04 two-sided
- Annual event rate of 7% for the placebo group
- Hazard ratio of 0.75 in favor of the elafibranor group
- 4% annual drop-out rate over 72 months
- Randomization ratio of 2:1 (elafibranor: placebo).

The 7% annual event rate in the placebo group is based on published literature on developing cirrhosis in patients with NASH and advanced fibrosis (F2-F3).[21,22,23,24,25] The rate of developing cirrhosis was estimated to be 7% (based on 8% per year in F3 patients and 6% per year in F2 patients). In a

conservative approach, no additional event rate was added for other events than histological cirrhosis or cirrhosis decompensation events. An annual clinical event/death rate of 7% was thus defined for the composite of both these endpoints.

There is no long-term randomized clinical trial in a NASH population with moderate and severe liver fibrosis. In the 72-week FLINT trial, the total drop-out rate was 6.7%.[35] Therefore, we estimate an approximate annual drop-out rate of 4%. Based on these assumptions, 456 events are required to provide 80% power to show that elafibranor is superior to placebo with respect to time to clinical event/death. In order to obtain 456 events, at least 2022 patients will be required in the IIT.

9.8. SAFETY ANALYSIS

Safety data (exposure, AEs, clinical laboratory tests, vital signs, and ECGs) will summarized by treatment group using descriptive statistics. The main summaries of safety will be based on the SS. Additional safety analysis will be based on the FSS and the exploratory F1 cohort. .

Adverse events will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA). An overall summary of AEs will be provided. The number and percentage of patients reporting AEs will also be presented by MedDRA System Organ Class and preferred term. The AEs will be summarized by worst severity and relationship to study drug. Serious AEs, and AEs leading to discontinuation will also be summarized. Narratives will be added for all SAE.

Clinical laboratory tests (hematology, chemistry, and urinalysis) recorded at each timepoint and change from baseline will be summarized by treatment group using descriptive statistics. Clinical laboratory values for each parameter will be assigned a classification according to whether the value is lower than, within, or higher than the reference range for that parameter. The values will then be summarized using shift tables to evaluate categorical changes from baseline to end of the 72 week treatment period with respect to reference ranges. The number and percentage of patients reporting markedly abnormal clinical laboratory values will also be summarized by treatment group.

Liver and kidney related laboratory tests including an assessment of DILI will also be summarized.

Vital signs recorded at each timepoint and change from baseline will be summarized by treatment group using descriptive statistics. The QTc and other ECG parameters recorded at each timepoint and change from baseline will also be summarized using descriptive statistics.

9.8.1. Interim analysis

The analysis of resolution of NASH without worsening of fibrosis will occur when approximately 50% of the F2 and F3 patients (i.e. 1023 patients) complete 72 weeks of treatment or discontinue early from the study. The null hypothesis will be tested at the two-sided 0.01 alpha level.

At this time, a snapshot of the database will be cleaned and locked for analysis and potential Subpart H or conditional approval submission. This analysis will be done by an unblinded team separate from the study team; the study team will not be unblinded until the final analysis at the end of follow-up.

The DSMB will also periodically review safety data from the study to ensure the well-being of study participants. These safety reviews will be based on reports generated by the SAC and may include select efficacy results so that the DSMB can assess the likely benefit-risk profile of elafibranor. These are not considered a formal interim analysis, and no type I error adjustments will be done for these reviews. Details will be in the DSMB Charter.

9.9. BLINDED REASSESSMENT

A blinded reassessment of the clinical event rate will be made when all patients have either completed or discontinued from the 72 week treatment period. The number of patients enrolled may be increased at this time and/or total duration extended. No adjustment will be made to the targeted number of events required for the final analysis of the long-term endpoint, so no adjustment for control of type I error should be required for this reassessment.

10. DATA HANDLING AND RECORD KEEPING

10.1. CRF AND SOURCE DOCUMENTS

A case report form (CRF) is required and should be completed for each screened patient. The completed eCRFs are the sole property of the Sponsor and should not be made available in any form to third parties, except for authorized Sponsor's representatives or appropriate regulatory authorities, without written permission from the Sponsor.

The Investigator will ensure that all data are entered promptly, legibly, completely, accurately and conform to source documents, in accordance with specific instructions accompanying the eCRFs designed specifically for this study. The CRF being used for this study is an electronic CRF that has been fully certified as being compliant with the FDA regulations at 21 Code of Federal Regulations (CFR) Part 11.

All study required patient data generated during the study will be recorded in the eCRF, with the exception of SAE forms and SF-36 which will be collected via ePRO. Patients will not be identified by name in the eCRF or on any study documents to be collected by the Sponsor (or designee), but will be identified by a patient number (patient initials will also be provided in the eCRF).

The Investigator will review and approve each completed eCRF; the Investigator's validation serving as attestation of the Investigator's responsibility for ensuring that all clinical and laboratory data entered in the eCRF are complete, accurate and authentic.

Should a correction be made, the corrected information will be recorded in the eCRF by the authorized person and explained (if necessary). All corrected data will be tracked through an audit trail.

It is the Investigator's obligation to ensure documentation of all relevant data in the patient's medical file (medical history, concomitant diseases, patient identification number, date of informed consent, visit dates, administration of study medication, AEs [start and stop dates] and all concomitant medications [start and stop dates]). All data recorded in the eCRF will be documented by source data.

10.2. RETENTION OF RECORDS

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified.

The Investigator will be provided with a study file, which should be used to file the Investigator Brochure, protocol/amendments, drug accountability records, sample informed consent, staff curriculum vitae, correspondence with the IRB/IEC, Sponsor, and other study-related documents.

To enable evaluations and/or audits from regulatory authorities or the Sponsor, the Investigator agrees to keep records, including the identity of all participating patients, all original signed ICFs, copies of all eCRFs, source documents, and detailed records of treatment disposition.

The Investigator must retain the study documentation until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. However these documents should be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the Sponsor. All hospital records will be archived according to local regulation.

The Sponsor should be notified if the Investigator relocates, retires, or for any reason withdraws from the trial. The trial records must be transferred to an acceptable designee, such as another Investigator, another institution, or to the Sponsor.

11. QUALITY CONTROL AND QUALITY ASSURANCE

11.1. QUALITY CONTROL & MONITORING PROCEDURES

It is the responsibility of the Investigator to ensure that the study is conducted in accordance with the protocol, Good Clinical Practice (ICH topic E6), applicable regulatory requirements, and the current Declaration of Helsinki (APPENDIX I – World Medical Association Declaration of Helsinki) and that valid data are entered into the eCRFs.

To achieve this objective, the Study Monitor's duties are to aid the Investigator and, at the same time, the Sponsor in the maintenance of complete, legible, well-organized, and easily retrievable data.

Before enrolling any patients in this study, the Study Monitor will review the protocol, the brochure for clinical investigators, the eCRFs and instructions for their completion and return, the procedure for obtaining informed consent, and the procedure for reporting AEs and SAEs with the Investigator. In addition, the Study Monitor will explain the Investigator's reporting responsibilities and all applicable regulations concerning the clinical evaluation of the study drug.

The Investigator will permit the representatives of Sponsor to monitor the study as frequently as the Sponsor deems is necessary to determine that data recording and protocol adherence are satisfactory. A Study Monitor from [redacted] Late Stage Development Services will be responsible for monitoring this clinical trial. To this end, the Study Monitor will visit the study site at suitable intervals and be in frequent contact through verbal and written communication. The eCRFs and related source documents, as well as drug accountability will be reviewed in detail by the monitor at each visit, in accordance with relevant SOPs and Good Clinical Practice (GCP; ICH topic E6) regulations. This includes results of tests performed as a requirement for participation in this study and any other medical records required to confirm information contained in the eCRFs, such as past medical history and secondary diagnoses.

A risk based monitoring strategy will be used for this study. Study monitoring strategy design will be based on overall study risk assessment. Individual site monitoring strategy design will be based on individual site risk assessment. On site monitoring will focus on source document verification of critical data and source document review of critical processes, and will be supported by formal remote site monitoring activities. Centralized monitoring activities will review study data to assess changes in individual site risk and to identify emerging trends, risks and issues across sites, countries, regions, and the global study. Further details can be found in the Monitoring Plan.

It is essential that the Study Monitor has access to all documents (related to the study and the individual participants) at any time these are requested. In turn, the Study Monitor will adhere to all requirements for patient confidentiality as outlined in the ICF. The Investigator and Investigator's staff will be expected to cooperate with the Study Monitor, to be available during a portion of the Monitoring Visit to answer questions, and to provide any missing information.

All monitoring activities will be reported and archived in the Trial Master File.

11.2. ETHICAL PRINCIPLES

This protocol complies with the principles laid down by the 18th World Medical Assembly (Helsinki, 1964) and all applicable amendments laid down by the World Medical Assemblies (APPENDIX I – World Medical Association Declaration of Helsinki), and the GCP guideline.

This trial also complies with applicable local regulatory requirements and laws of each country in which the study is performed, as well as any applicable guidelines.

11.3. QUALITY ASSURANCE

For the purpose of ensuring compliance with the protocol, GCP and applicable regulatory requirements, the Investigator should permit auditing by the Sponsor and inspection by applicable regulatory authorities. The Investigator agrees to allow the auditors/inspectors to have direct access to his/her study records for review, being understood that these personnel will adhere to all requirements for patient confidentiality, and as such will not disclose any personal identity or personal medical information.

As soon as the Investigator is notified of a future inspection by the Authorities, he/she will inform the Sponsor and authorize the Sponsor to participate at this inspection.

The confidentiality of the data verified and the anonymity of the patients should be respected during these inspections.

Clinical data associates from the Sponsor's representative will review the data for completeness and logical consistency. Additionally, the clinical data associates will use automated validation programs to help identify missing data, selected protocol violations, out of range data, and other data inconsistencies. Requests for data clarification or correction will be electronically provided to the investigative site for resolution. Clinical data associates will assure that corrections have been applied properly.

12. ETHICS AND REGULATORY

12.1. INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE

The GCP guidelines and the US CFR Title 21 Section 56 (21 CFR 56) require that approval must be obtained from an Independent Ethics Committee (IRB/IEC) prior to participation of human patients in research studies. Prior to the study onset, the protocol, ICF, advertisements to be used for patient recruitment, and any other written information regarding this study to be provided to the patient or the patient's legally acceptable representative must be approved by the IRB/IEC. The Sponsor will supply relevant material for the Investigator to submit to the IRB/IEC for the protocol's review and approval. Verification of the IRB's unconditional approval of the protocol and the written ICF statement will be transmitted to the Investigator. Documentation of the relevant IRB/IEC approval and of the IRB/IEC compliance with GCP guideline will be maintained by the site and will be available for review by the Sponsor or its designee or by the authorized members of regulatory agencies.

The Applicant must supply the Sponsor with written documentation of the initial favorable opinion of the clinical research before the start of the trial.

The study will not commence until favorable opinion has been obtained from the appropriate IRB/IEC.

If any alterations, others than changes of administrative nature only, are made to the study protocol, a formal protocol amendment will be issued. The IRB/IEC will be informed by the Investigator of subsequent protocol amendments and of SUSARs. Approval for protocol amendments will be transmitted in writing to the Investigator.

The amendment will not be implemented until IRB/IEC approval, except in cases where immediate implementation is necessary to eliminate or prevent imminent hazard to the patients. A protocol change intended to eliminate an apparent immediate hazard must be documented in an amendment, reported to the IRC/IEC within 5 working days, and submitted to the appropriate regulatory agencies in the required time frame.

If requested, the Investigator will permit audits by the IRB/IEC and regulatory inspections by providing direct access to source data/documents.

The Investigator will provide the IRB/IEC with progress reports at appropriate intervals (not to exceed one year) and a Study Progress Report following the completion, termination, or discontinuation of the Investigator's participation in the study.

12.2. COMPETENT AUTHORITY

In the same way as for IRB/IEC (see Section 12.1), when required by national regulation, approval from Competent Authorities (CA) should be granted before the beginning of the study. If applicable, Amendments will also be submitted to CA for approval.

12.3. PATIENT INFORMATION AND CONSENT

Written informed consent for the study will be obtained from each patient before protocol-specific procedures are carried out. The ICF used by the Investigator for obtaining the patient's Informed Consent must be reviewed and approved by the Sponsor prior to submission to the appropriate ethics committee (IRB/IEC). The ICF will be approved (along with the protocol) by the IRB/IEC.

In the case of any exploratory substudies, specific study documents will be prepared and IRB/IEC and authority approvals shall be obtained when applicable.

The Investigator or a person designated by the Investigator (according to applicable regulatory requirements), will explain the nature of the study and the action of the test product. The patients will be informed that participation is voluntary and that they can withdraw from the study at any time. In accordance with 21 CFR 50, the informed consent process shall be documented by the use of a written ICF approved by the designated IRB/IEC and will be signed and personally dated by the patient or by the patient's legally acceptable representative and by the person who conducted the informed consent discussion prior to protocol-specific procedures being performed. A separate consent form will be obtained for optional genetic and biomarker samples to be stored in the blood bank.

The Investigator must maintain the original, dated and signed ICF. A copy of the signed ICF must be given to the patient.

12.4. PATIENT CONFIDENTIALITY

The Sponsor will affirm and uphold the principle of the patient's right to protection against the invasion of privacy. Throughout this study and any subsequent data analyses, all data will be identified only by protocol number and patient number.

All unpublished information that the Sponsor gives to the Investigator shall be kept confidential and shall not be published or disclosed to a third party without the prior written consent of the Sponsor.

When the Sponsor generates reports for presentations to regulatory agencies, one or more of the Investigators who has/have contributed significantly to the study will be asked to endorse the final report. The endorsement is required by some regulatory agencies.

The Investigator shall not make a patent application based on the results of this study and shall not assist any third party in making such an application without the written authorization of the Sponsor unless otherwise specified in the CSA.

12.5. DEFINITION OF THE END OF THE RESEARCH

End of the research corresponds to the end of participation (end of study EOT Visit) of the last patient participating in the research.

13. FINANCING AND INSURANCE

13.1. FINANCIAL ISSUES

Financial contracts will be signed between the Sponsor and the Investigator/Institution before initiation of the study.

13.2. INSURANCE AND PATIENT INJURY

The patients taking part in the trial will be covered by the insurance taken by the Sponsor for this trial, if they were to suffer any prejudice as a result of taking part in the trial.

In general, if a patient is injured as a direct result of the study drug, the Sponsor will pay for reasonable and necessary medical treatment for the injury, to the extent the expenses are not covered by the patient's medical insurance, a government program, or other responsible third party. If laws or regulations of the locality in which the trial is taking place require additional payment of expenses, the Sponsor shall comply with such law or regulation.

The Sponsor certifies to have taken out an insurance policy to cover the financial consequences of its civil liability and that of everyone involved in the research, and notably that of the Investigators and their colleagues with regard to any accidents or damage concerning the administration of the drug or paraclinical examinations directly linked to the performance of the trial.

14. STUDY RESULTS AND PUBLICATION POLICY

14.1. STUDY REPORT

The final report will be written in ENGLISH upon completion of study and statistical analysis according to ICH E3 guideline. The report or part of it must be submitted to relevant authorities if applicable.

[redacted] will prepare an integrated clinical and safety report. Prior to issuing the final CSR, [redacted] will prepare a draft report for approval by the Sponsor. The report will be in accordance with the ICH E3 Guideline for Industry: Structure and Content of CSRs. The draft report will be submitted for Quality Assurance audit, the findings of which will be incorporated into the final version.

An electronic copy of the final CSR will be made available to the Sponsor. The study report will be provided in PDF and MS Word formats unless agreed otherwise by [redacted] Reports requiring specialized Sponsor formats/alternative computer software packages may be possible on request from the Sponsor but may involve extra time and cost. Electronic datasets will also be provided to the Sponsor on issuance of the final report.

After review by the Sponsor, a final CSR will be submitted to the Sponsor which incorporates the Sponsor's comments.

14.2. CONFIDENTIALITY AND OWNERSHIP OF DATA, USE OF THE STUDY RESULTS AND PUBLICATION

All materials, information (oral or written), and unpublished documentation provided to the Investigators (or any company/institution acting on their behalf), including this protocol, the patient CRFs, and the Investigator's Brochure, are the exclusive property of the Sponsor and may not be published, given, or disclosed, either in part or in whole, by the Investigator or by any person under his/her authority to any third party without the prior express consent of the Sponsor.

However, the submission of this protocol and other necessary documentation to the ethics committee (IRB/IEC) and the Competent Authority is expressly permitted, their members having the same obligation of confidentiality.

The Investigator shall consider all information, results, discoveries, records (accumulated, acquired, or deduced) in the course of the study, other than that information to be disclosed by law, as confidential and shall not disclose any such results, discoveries, or records to any third party without the Sponsor's prior written consent.

The Sponsor retains exclusive ownership of all data, results, reports, findings, discoveries, and any other information collected during this study. Therefore, the Sponsor reserves the right to use the data from the present study, either in the form of Case Report Forms (or copies of these), or in the form of a report, with

or without comments and with or without analysis, in order to submit them to the Health Authorities of any country.

When the Sponsor generates reports for presentations to regulatory agencies, one or more of the Investigators who has/have contributed significantly to the study will be asked to endorse the final report. The endorsement is required by some regulatory agencies.

Furthermore, in the event that the study generates patentable results, the Investigator (or entity acting on his/her behalf according to local requirements) shall refrain from filing patent application(s) on such results, which will be filed by the Sponsor or its designees in its own name and at its expense.

Clinical study will be registered on the open access website http://www.clinicaltrials.gov before the screening of the first patient in the study.

It is the policy of the Sponsor to encourage the presentation and/or publication of the results of their studies, using only clean, checked, and validated data in order to ensure the accuracy of the results.

The publication of study results will be agreed between the Sponsor and the Investigators.

At least 45 days in advance of proposed submission, the Investigator should forward a copy of the manuscript or abstract for review by the Sponsor, and, if necessary, delay publication or communication for a limited time in order to protect the confidentiality or proprietary nature of any information contained therein. The Sponsor may also request that the Sponsor's name and/or names of one or several of its employees appear or not appear in such publication.

15. REFERENCES LIST

1. Day CP, James OF. Steatohepatitis: a tale of two "hits"? *Gastroenterology*. 1998;114:842-845.
2. Jou J, Choi SS, Diehl AM. Mechanisms of disease progression in nonalcoholic fatty liver disease. *Semin Liver Dis*. 2008;28: 370-379.
3. Edmison J, McCullough AJ. Pathogenesis of nonalcoholic steatohepatitis: human data. *Clin Liver Dis*. 2007;11:75-104.
4. Browning JD, Horton JD. Molecular mediators of hepatic steatosis and liver injury. *J Clin Invest*. 2004;114:147-152.
5. Ikejima K, Honda H, Yoshikawa M, et al. Leptin augments inflammatory and profibrogenic responses in the murine liver induced by hepatotoxic chemicals. *Hepatology*. 2001;34: 288-297.
6. Poniachik J, Santiban˜ez C, Haim D, et al. Enhancement in liver nuclear factor-kb (nf-kb) and activator protein 1 (ap-1) DNA binding in obese patients with nonalcoholic fatty liver disease. The 43rd Annual Meeting of the European Association for the Study of the Liver. Milan, Italy, 2008.
7. Yamauchi T, Kamon J, Minokoshi Y, et al. Adiponectin stimulates glucose utilization and fatty-acid oxidation by activating AMP-activated protein kinase. *Nat Med*. 2002;8(11):1288-95. Epub 2002 Oct 7.
8. Targher G, Bertolini L, Rodella S, et al. Associations between plasma adiponectin concentrations and liver histology in patients with nonalcoholic fatty liver disease. *Clin Endocrinol (Oxf).* 2006;64:679-683.
9. Xu H, Barnes G, Yang Q, et al. Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance. *J Clin Invest*. 2003;112(12):1821-1830.
10. Pessayre D, Fromenty B, Mansouri A. Mitochondrial injury in steatohepatitis. *Eur J Gastroenterol Hepatol*. 2004;16:1095-1105.
11. Crespo J, Cayon A, Fernandez-Gil P, et al. Gene expression of tumor necrosis factor alpha and TNF-receptors, p55 and p75, in nonalcoholic steatohepatitis patients. *Hepatology*. 2001;34:1158–1163.
12. Hotamisligil GS, Arner P, Caro JF, et al. Increased adipose tissue expression of tumor necrosis factor-alpha in human obesity and insulin resistance. *J Clin Invest.* 1995;95:2409-2415.
13. Ramalho RM, Cortez-Pinto H, Castro RE, et al. Apoptosis and Bcl-2 expression in the livers of patients with steatohepatitis*. Eur J Gastroenterol Hepatol*. 2006;18:21-29.
14. Laurin J, Lindor KD, Crippin JS, et al. Ursodeoxycholic acid or clofibrate in the treatment of nonalcohol-induced steatohepatitis: a pilot study. *Hepatology*. 1996;23(6):1464-1467.
15. Shan W, Nicol CJ, Bility MT, et al.,Peroxisome proliferator-activated receptor-beta/delta protects against chemically induced liver toxicity in mice, *Hepatology*. 2008;47(1):225-235.
16. Risérus U, Sprecher D, Johnson T, et al. Activation of peroxisome proliferator-activated receptor (PPAR) delta promotes reversal of multiple metabolic abnormalities, reduces oxidative

stress, and increases fatty acid oxidation in moderately obese men. *Diabetes*. 2008;57(2):332-339. Epub 2007 Nov 16.

17. Kang K, Reilly SM, Karabacak V, et al. Adipocyte-derived TH2 cytokines and myeloid PPAR delta regultate macrophage polarization and insulin sensitivity. *Cell. Metab.* 2008;7:485-495.
18. Odegaard JI, Ricardo-Gonzalex RR, Red Eagle A et al. Alternative M2 activation of Kupffer cells by PPARδ ameliorates obesity induced insulin resistance. *Cell. Metab*. 2008;7:496-507.
19. Cattley RC, Deluca j, Elcombe C, et al. Do peroxisome proliferating compounds pose a hepatocarcinogenic hazard to humans? *Regul Toxicol Pharmacol*. 2008;27(1 Pt 1):47-60.
20. Musso G, Gambino R, Cassader M, Pagano G . Meta-analysis: natural history of nonalcoholic fatty liver disease (NAFLD) and diagnostic accuracy of non-invasive tests for liver disease severity. *Ann Med*. 2011;43(8):617-649.
21. Ekstedt M, Franzen LE, Mathiesen UL, et al. Long-term follow-up of patients with NAFLD and elevated liver enzymes. *Hepatology.* 2006;44(4):865-873.
22. Angulo P, Kleiner DE, Dam-Larsen S, et al. Liver Fibrosis, but No Other Histologic Features, Is Associated With Long-term Outcomes of Patients With Nonalcoholic Fatty Liver Disease. *Gastroenterology.* 2015;149(2):389-397 e310.
23. Argo CK, Northup PG, Al-Osaimi AM, Caldwell SH . Systematic review of risk factors for fibrosis progression in nonalcoholic steatohepatitis. *J Hepatol*. 2009;51(2):371-379.
24. Pagadala MR, McCullough AJ. The relevance of liver histology to predicting clinically meaningful outcomes in nonalcoholic steatohepatitis. *Clin Liver Dis* 2012;16(3):487-504.
25. Singh S, Allen AM, Wang Z, Prokop LJ, Murad MH, Loomba R. Fibrosis progression in nonalcoholic fatty liver vs nonalcoholic steatohepatitis: a systematic review and meta-analysis of paired-biopsy studies. *Clin Gastroenterol Hepatol.* 2015;13(4):643-654.
26. Hashimoto E, Tokushige K. Prevalence, gender, ethnic variations, and progression of NASH. *J Gastroenterol.* 2011;46(supplement 1):63-69.
27. Younossi ZM, Stepanova M, Rafiq N, et al. Pathologic criteria for nonalcoholic steatohepatitis: interprotocol agreement and ability to predict liver-related mortality. *Hepatology.* 2011;53(6):1874-1882.
28. Ratziu V, de Ledinghen V, Oberti F, et al. A randomized controlled trial of high-dose ursodesoxycholic acid for nonalcoholic steatohepatitis. *J Hepatol.* 2011;54(5):1011-1019.
29. Sanyal AJ, Brunt EM, Kleiner DE, et al. Endpoints and clinical trial design for nonalcoholic steatohepatitis. *Hepatology*. 2011;54:344-353.
30. Sanyal AJ, Friedman SL, McCullough AJ, et al. Challenges and opportunities in drug and biomarker development for nonalcoholic steatohepatitis: findings and recommendations. *Hepatology.* 2015;61(4):1392-1405.
31. McPherson S, Hardy T, Henderson E, et al. Evidence of NAFLD progression from steatosis to fibrosing-steatohepatitis using paired biopsies: implications for prognosis and clinical management. *J Hepatol*. 2015;62(5):1148-1155.

32. Dunn W, Xu R, Wingard DL, et al. Suspected nonalcoholic fatty liver disease and mortality risk in a population-based cohort study. *Am J Gastroenterol.* 2008;103(9):2263-2271.
33. Rafiq N, Bai C, Fang Y, et al. Long-term follow-up of patients with nonalcoholic fatty liver. *Clin Gastroenterol Hepatol.* 2009;7(2):234-328.
34. Clinical Trial Facilitation Group (2014). Recommendations related to contraception and pregnancy testing in clinical trials. Available at: http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf
35. Neuschwander-Tetri BA, Loomba R, Sanyal AJ, et al. Farnesoid X nuclear receptor ligand obeticholic acid for non-cirrhotic, nonalcoholic steatohepatitis (FLINT): a multicentre, randomised, placebo-controlled trial. *Lancet*. 2015;385(9972):956-965.

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Appendices

APPENDIX I – WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964
and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words,

"The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by

individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and

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standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

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27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain

for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made

publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

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APPENDIX II: ADEQUATE DIET AND LIFESTYLE RECOMMENDATIONS

Essential Components of Therapeutic Lifestyle Changes (TLC)

Component	Recommendation
LDL-raising nutrients	
Saturated fats*	Less than 7% of total calories
Dietary cholesterol	Less than 200 mg/day
Therapeutic options for LDL lowering	
Plant stanols/sterols	2 grams per day
Increased viscous (soluble) fiber	10–25 grams per day
Total calories (energy)	Adjust total caloric intake to maintain desirable body weight/prevent weight gain
Physical activity	Include enough moderate exercise to expend at least 200 kcal per day

* *Trans* fatty acids are another LDL-raising fat that should be kept at a low intake.

Macronutrient Recommendations for the TLC Diet

Component	Recommendation
Polyunsaturated fat	Up to 10% of total calories
Monounsaturated fat	Up to 20% of total calories
Total fat	25–35% of total calories*
Carbohydrate†	50–60% of total calories*
Dietary fiber	20–30 grams per day
Protein	Approximately 15% of total calories

* ATP III allows an increase of total fat to 35 percent of total calories and a reduction in carbohydrate to 50 percent for persons with the metabolic syndrome. Any increase in fat intake should be in the form of either polyunsaturated or monounsaturated fat.
† Carbohydrate should derive predominantly from foods rich in complex carbohydrates including grains—especially whole grains—fruits, and vegetables.

APPENDIX III: PERMITTED/NON-PERMITTED MEDICATION

Table I: NON-PERMITTED MEDICATION AND CONDITION

Medications	**When**
Same pharmacological class (PPAR agonists)	
Thiazoledinediones (glitazones)	From 6 months prior to liver biopsy* up to end of study treatment (EOT) Visit
Fibrates	From 2 months prior to Randomization up to EOT Visit
Medication that may induce steatosis/steatohepatitis	
Corticosteroids (parenteral & oral chronic administration)	From 30 days prior to first Screening Visit up to EOT Visit
Amiodarone	
Tamoxifen	
Methotrexate	
Medication that may interact with absorption, metabolism, etc	
Indomethacin	From Randomization up to EOT Visit

* Given the potential effect on diagnostic liver biopsy of patients previously treated by glitazones

Table II: PERMITTED MEDICATION AND CONDITION

Medications	When
Antidiabetic therapy	
Conditions upon inclusion	
GLP-1 agonist	Dose stability required from at least 6 months prior to the inclusion liver biopsy up to EOT Visit
All other ATD therapy (insulin, sulfamides, metformin, gliptins, SGLT2-inhibitors	No qualitative change (i.e. no implementation of a new drug) from at least 6 months prior to the inclusion liver biopsy up to EOT Visit
Conditions during the study	
GLP-1 agonist	Initiation of these therapies is prohibited during the study up to EOT Visit
Glitazones	
Lipid lowering therapy	
Statins	Dose stability required from at least 2 months prior to Screening up to EOT Visit
Ezetimibe	
Others	
Vitamin E >400 IU/day	Dose stability required from at least 6 months prior to the inclusion liver biopsy up to EOT Visit
PUFAs >2 g/day	
Ursodeoxycholic acid	

Abbreviations: ATD = autoimmune thyroid disease; EOT = end of study treatment; PUFA = polyunsaturated fatty acids; SGLT2 = sodium/glucose cotransporter 2.

APPENDIX IV: ALCOHOL COMPARISON TABLE

Alcohol type	Alcohol by volume (ABV)	Volume		Amount of alcohol	
		Fluid ounce	mL	Units [2]	grams
Beer	3.5%	12	350	0.7	9.8
Beer	5%	12	350	1	14
Cider	7%	12	350	1.4	19.6
Distilled spirits or liquor [1]	40%	1.5	45	1	14
Wine	12%	5	150	1	14

1. e.g., gin, rum, vodka, whiskey.
2. Units calculated using the cleave Books calculator for units of drink, using the US definition of 1 unit of alcohol as 17.7 mL (14.0 g) of pure alcohol (http://www.cleavebooks.co.uk/scol/ccalcoh3.htm).

APPENDIX V: PRODUCT CARTON AND WALLET LABELING

	Carton	Wallet
Protocol number	X	X
Sponsor details	X	X
Site number	X	X
Subject ID	X	X
Kit number	X	X
Visit number	X	-
Lot number	X	X
Expiry date	X	X
Contents	X	X
Route of administration	X	X
Administration instructions	X	X
"For Clinical Trial Use only."	X	X
"Keep out of reach of Children."	X	X
Storage details	X	X
Instructions for product and package return at next visit	X	X

GENFIT
TOWARDS BETTER MEDICINE

CLINICAL PROTOCOL – PHASE 3

Protocol N° GFT505-315-1

EudraCT N°2015-005385-38

IND number: 115028

Amendment 1: Final 2.0 – Release date 06 January 2017

Supersedes previous Version 1.0 - Release date: 15 January 2016

A Multicenter, Randomized, Double-Blind, Placebo-Controlled Phase III Study to Evaluate the Efficacy and Safety of Elafibranor in Patients with Nonalcoholic Steatohepatitis (NASH) and fibrosis

International Coordinating Investigator Committee	[redacted]	[redacted]
Sponsor	**GENFIT**	Parc Eurasanté 885, Avenue Eugène Avinée 59120 LOOS, France
Represented by:	[redacted]	[redacted]

CLINICAL STUDY PROTOCOL SIGNATURE PAGE

Protocol N°: **GFT505-315-1 / EudraCT N° 2015-005385-38/ IND n°115028**

Version number: **2.0**

Release date: **06 January 2017**

TITLE: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Phase III Study to Evaluate the Efficacy and Safety of Elafibranor in Patients with Nonalcoholic Steatohepatitis (NASH) and fibrosis.

In signing below, I give agreement to the protocol.
International Coordinators:

[redacted]

[redacted]

Signature

[redacted]

Date (dd-mmm-yyyy)

CLINICAL STUDY PROTOCOL SIGNATURE PAGE

Protocol N°: **GFT505-315-1 / EudraCT N° 2015-005385-38/ IND n°115028**

Version number: **2.0**

Release date: **06 January 2017**

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In signing below, I give agreement to the protocol.

[redacted]

[redacted]

Date (dd-mmm-yyyy)

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[redacted]

[redacted]

Signature

[redacted]

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In signing below, I give agreement to the protocol.

On behalf of (the Sponsor): GENFIT
Parc Eurasanté
885, Avenue Eugène Avinée
59120 LOOS – France

Name: [redacted]

[redacted]

Signature

[redacted]

Date (dd-mmm-yyyy)

CLINICAL STUDY PROTOCOL

INVESTIGATOR SIGNATURE PAGE

PROTOCOL TITLE: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Phase III Study to Evaluate the Efficacy and Safety of Elafibranor in Patients with Nonalcoholic Steatohepatitis (NASH) and fibrosis.

PROTOCOL NUMBER: GFT505-315-1

EudraCT Number: 2015-005385-38

IND Number: 115028

CLINICAL PHASE: III

VERSION: 2.0

DATE: January 06, 2017

SPONSOR: GENFIT,
Parc Eurasanté,
885 Avenue Eugène Avinée,
59120 LOOS - France

In signing below, I confirm having read the protocol, and give agreement to the protocol.

INVESTIGATOR NAME: _____

INSTITUTION NAME: _____

INSTITUTION ADDRESS: _____

_____

SIGNATURE: _____

DATE: _____ /_____ /_____

Day Month Year

STUDY CONTACTS

Protocol N°: **GFT505-315-1/ EudraCT N° 2015-005385-38/ IND n° 115028**

International Coordinating Investigator Committee	[redacted]	[redacted]
Sponsor	GENFIT	Parc Eurasanté 885, Avenue Eugène Avinée 59120 LOOS - France
CRO for monitoring, data management & statistics	[redacted]	[redacted]
Pharmacovigilance	[redacted]	[redacted]

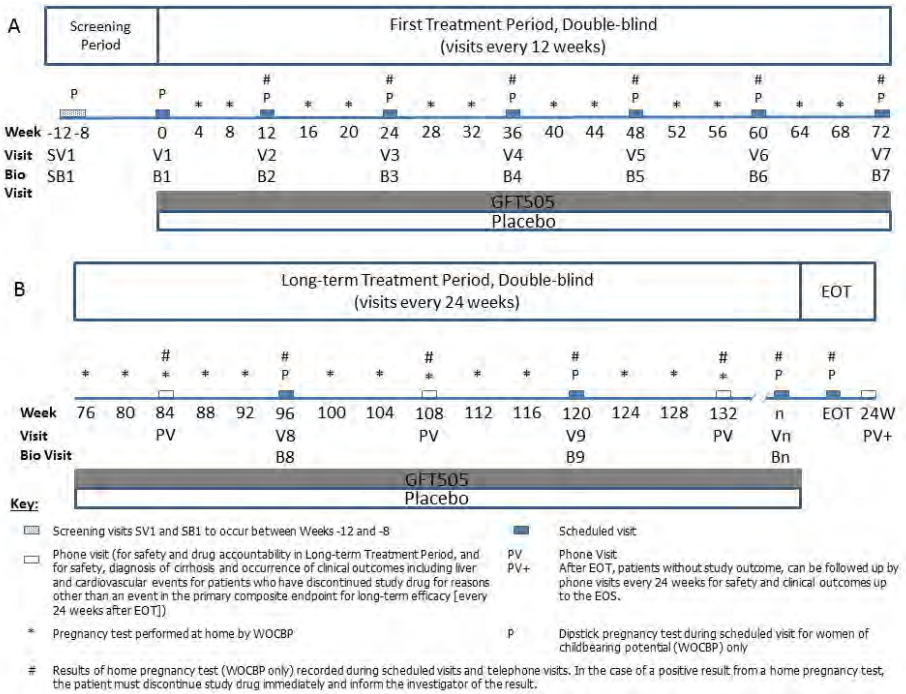
IXRS	[redacted]group.com
Study drug supplier	[redacted]
Central laboratory	[redacted]
Central pathology laboratory	[redacted]
ePRO	[redacted]

AMENDMENT 1: 06 JANUARY 2017

Amendment 1 addresses inconsistencies in the original protocol and increases clarity. It also details the statistical analyses to be consistent with the Statistical Analysis Plan. Revisions were made to protocol sections noted below as well as to the study synopsis, the study general assessment schedule (Table 1), study biological assessment schedule (Table 2), study duration and visit schedule (Figure 1), and throughout the protocol text as required. Added text is **bolded**; deleted text is ~~struck through~~.

Summary of major changes to the protocol:

Section	New Text
Table 2: STUDY BIOLOGICAL ASSESSMENT SCHEDULE (amendments not described anywhere else in protocol)	***Screening Visit 1 - chemistry panel*** *HbA1c[3,2], fasting plasma glucose, Insulin (fasting), HOMA –IR, creatinine, eGFR[3], GGT, AST, ALT, CPK[3,2], alkaline phosphatase,* ***total and conjugated bilirubin, sodium****,* ~~*and*~~ *TG,* ***and MELD score***
	V1 to Vn total chemistry panel *HbA1c, fasting plasma glucose, creatinine, eGFR, GGT, AST, ALT, CPK, alkaline phosphatase, total proteins, albumin, electrolytes (sodium, potassium, chloride, calcium), uric acid, urea (BUN), total and conjugated bilirubin, hsCRP, total cholesterol, nonHDL-C, HDL-C, TG, calculated VLDL-C, ApoAI, ApoB,* ~~*and*~~ *calculated LDL-C,* ***and MELD score***
	5. Whole blood sample will be only taken at SV1 ~~for the analysis of PNPLA3 following DNA extraction. Plasma~~ **while plasma** and serum samples **are to be taken** ~~should be retrieved~~ at every visit ONLY for patients who have signed the **pharmacogenomics** ~~genetic~~ and biomarker ICF.

Section	**New Text**
Figure 2: **PREGNANCY TESTING SCHEDULE FOR WOMEN OF CHILDBEARING POTENTIAL**	New figure included for pregnancy testing schedule for women of childbearing potential. Appropriate text added throughout protocol as required. 
Section 1.9.2 Primary endpoint for clinical outcome (postapproval confirmation)	The primary endpoint of the Long-term Treatment Period **(LTTP)** of the study is to evaluate the effect of elafibranor on **the progression to cirrhosis,** all-cause mortality**,** and liver-related clinical outcomes as measured by the **onset** ~~time to first occurrence~~ of any of the listed adjudicated events (clinical outcomes composite endpoint).

Section	**New Text**
Section 1.11 Rationale for safety monitoring	Given the known effect of elafibranor on serum creatinine increase, special attention will be paid to all the renal safety markers (plasmatic or urinary parameters), including but not limited to albumin-creat**in**ine ratio~~n~~, cystatin C, neutrophil gelatinase-associated lipocalin (N-Gal), N acetyl β D -glucosaminidase β-NAG, kidney injury molecule-1 (KIM 1). Serum creatinine,~~ and~~ **modification of diet in renal disease (MDRD) derived estimated glomerular filtration rate (eGFR)** ~~creatinine clearance~~, and **the** results of urinalysis (dipstick) will be reported at each visit, as well as blood urea nitrogen.
Section 2.1.2 Long-term endpoint **Note:** this change was also implemented in Section 3.10 and Section 9.2.2	• ~~Hospitalization (as defined by a stay of 24 hours or greater) for new onset or recurrence~~ **The onset** of: o variceal bleed o hepatic encephalopathy o spontaneous bacterial peritonitis o ~~uncontrolled~~ ascites o hepatorenal syndrome o hepatopulmonary syndrome o chronic gastrointestinal blood loss due to portal hypertensive gastropathy (provided that these lead to hospitalization or transfusion).
Section 3.6.1 Screening visits SV1 (Week -12 to Week -8) and SV2 (Week -12 to Week -4):	• Signature of informed consent witnessed by the Investigator or designated person. **Note: The signature of the informed consent may also be performed before SV1.** • Check concomitant/prior medication (within ~~30 days~~ **6 months** prior to Screening) (described in Section 7.12 and APENDIX III: Permitted/non-permitted medication) • Check if a liver biopsy with confirmed NASH and fibrosis is available, and, if so send sample for central confirmation of NASH diagnosis (described in Section 6.1.1.2). This historical diagnostic biopsy should be obtained within 6 months prior to the ~~planned Randomization~~

Section	**New Text**
	Screening Visit ~~(V1)~~. ~~For DILI adjudication, in order to define an adequate baseline value for the liver parameters (AST, ALT, total bilirubin, INR), at least 2 consecutive assessments in at least 8 weeks apart between visit SV1 and V1 should be performed~~. Visits SV1 and V1 should be scheduled **at least 8 weeks apart in order to have 2 consecutive baseline values of AST, ALT, total bilirubin, and INR for DILI adjudication (using SV1 and V1 kits)**.~~according to this requirement.~~ **In case of known cured hepatitis C virus (HCV) infection, HCV RNA testing can be done at SV1 without waiting for HCV Ab results.** If needed, a retesting of abnormal HbA1c, ~~estimated glomerular filtration rate (eGFR),~~ or creatine phosphokinase (CPK) results or additional testing of ~~hepatitis C virus (~~HCV~~)~~ RNA, may be performed during the screening window to determine the eligibility for the study as described in exclusion criteria 5, ~~13,~~**12**, 30, and **31** ~~32~~ (see Section 4.2 and Section 3.11). At visit SV1, preliminary entrance criteria will be reviewed. Potentially eligible patients will be asked if they agree to participate in the study and sign the ICF. Each patient who ~~will have~~ **has** signed the ICF will be allocated a patient number composed of ~~7~~**9** digits which is generated by the IXRS. ➢ First 3 digits corresponding to the ISO numeric country code (this number will be predefined), ➢ Next ~~2~~**3** digits corresponding to the site number (this number will be predefined), ➢ Last ~~2~~**3** digits corresponding to the numerical order of the patient entry at the study site.
Section 3.7.2 First Treatment Period visits V1 to V7 (Week 0 to Week 72)	The following procedures will be performed at each of the 12 week visits from V1 to V7 : • **Provision of home pregnancy test kits (for WOCBP only)** • **Record result of home pregnancy tests (to be performed every 4 weeks [see Figure 2]) since previous visit (for WOCBP only, every visit from V1**

Section	**New Text**
Section 3.8.1 Long-term Treatment Period Visits (V8 to Vn)	The following procedures will be performed at each visit from V8 to Vn: • Quality of life assessment (V8, V9, V11, and **every** 48 ~~weekly~~ **weeks** thereafter Section 6.2.6) • **Provision of home pregnancy test kits (for WOCBP only)** • **Record result of home pregnancy tests (to be performed every 4 weeks [see Figure 2]) since previous visit (for WOCBP only, every visit from V1**
Section 3.8.2 Long-term Treatment Period phone visits (PV1 to PVn)	Phone visits will be scheduled every 24 weeks starting 12 weeks after Visit 7 for data collection on **diet and lifestyle**, **concomitant medications**, clinical outcomes, safety, **home pregnancy test results**, and IP compliance control. If any information during this phone contact requires a visit, the Investigator may decide to perform an unscheduled visit (described in Section 3.11.2). IXRS registration will be performed for each phone visit.
Section 3.9 End of Study Treatment Visit	**The patient will be contacted at least 1 week before the visit to be reminded of procedures and IP return (if required).** The following procedures will be performed at the EOT Visit: • IXRS registration • Physical examination (described in Section 6.2.1) • Record vital signs and weight (described in Section 6.2.1 and Section 6.2.3) • **Confirmation of adequate diet and lifestyle compliance (described in Section 5.1.1 and APPENDIX II: Adequate diet and lifestyle recommendations), alcohol restrictions (described in Section 5.1.2), and tobacco habits** • Check concomitant/prior medication (described in Section 7.12 and APPENDIX III: Permitted/non-permitted medication) • Quality of life assessment (described in Section 6.2.6) • Check AEs and occurrence of any clinical outcome(described in Section 6 and Section 8) • Blood samples (described in Table 2)

Section	**New Text**
	• Plasma & serum bank samples (only if additional genetic and biomarker ICF informed consent signed) • Urinalysis and urinary dipstick (described in Table 2) • **Urinary pregnancy test (for WOCBP only)** • **Record results of home pregnancy tests (to be performed every 4 weeks [see Figure 2) since previous visit (for WOCBP only)** • **Record waist circumference** • 12-lead ECG (described in Section 6.2.4) • Drug accountability.
3.11.1 Retesting screening visits	Permitted retesting or additional testing in case of abnormal value at SV1 are: • CPK: can be repeated prior to Randomization (V1) within 1 to 2 weeks after initial test. • ~~eGFR measurement: can be repeated prior to Randomization (V1) within the following timeframe: minimum 4 weeks after initial test and maximum 2 weeks prior to planned Randomization.~~ • HCV RNA testing: in case positive HVC Ab test **at SV1** required latest 2 weeks prior to Randomization (V1). • HbA1c: can be repeated at the latest 2 weeks prior to Randomization (V1). **Any other retest deemed necessary by the Investigator should be discussed with the Study Medical Monitors.**
Section 4.1 Inclusion criteria	~~3. BMI ≤45 kg/m^2~~ **3.** Females participating in **this** ~~the~~ **study must** ~~either not~~ **be of nonchildbearing potential** ~~(hysterectomy, bilateral oophorectomy, medically documented ovarian failure, or >50 years of age with~~ **or using highly efficient contraception for the full duration of the study and for 1 month after the end of treatment, as described below:** ○ Cessation of menses for at least 12 months due to ovarian failure~~) or using efficient double contraception; hormonal,~~

Section	New Text
	○ **Surgical sterilization such as bilateral oopherectomy, hysterectomy, or medically documented ovarian failure** ○ **If requested by local IRB regulations and/or National laws, sexual abstinence may be considered adequate (the reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient)** ○ **Using a highly effective nonhormonal method of** contraception (~~including patch, contraceptive ring, etc~~ **bilateral tubal occlusion, vasectomized partner or** intra-uterine device~~, or opther mechanical~~**)** ○ **Double** contraception ~~method + condom or diaphragm~~ **with barrier AND highly effective hormonal method of contraception (oral, intravaginal** or ~~spermicide for the full duration of the study and for 1 month after the end of treatment~~ **transdermal combined estrogen and progestogen hormonal contraception associated with inhibition of ovulation; oral, injectable or implantable progestogen-only hormonal contraception associated with inhibition of ovulation; or intrauterine hormone-releasing system). The hormonal contraception must be started at least 1 month prior to Randomization.** **9. For patients with type 2 diabetes, glycemia must be controlled. If glycemia is controlled by antidiabetic drugs, change in anti-diabetic therapy must follow these requirements:** ○ **no qualitative change 6 months prior to diagnostic liver biopsy up to Randomization (i.e., implementation of a new anti-diabetic therapy) for patients treated with metformin, gliptins, sulfonylureas, sodium/glucose cotransporter (SGLT) 2 inhibitors, glucagon-like peptide (GLP)-1 agonists, or insulin. Dose changes of these medications are allowed in the 6 months prior to diagnostic liver biopsy, except for GLP-1 agonists, which must remain on stable dose in the 6 months prior to diagnostic liver biopsy.** ○ **no implementation of GLP-1 agonists and SGLT2 inhibitors up to 72 weeks of treatment (V7).** **Initiation of any other antidiabetic drugs is allowed after Randomization based on treating physicians' judgment, except for glitazones which are prohibited 6 months prior to diagnostic liver biopsy until the end of treatment.** ~~10. For patients with type 2 diabetes, glycemia must be controlled. If glycemia is controlled by anti diabetic drugs, no change is allowed~~

Section	**New Text**
	~~within 6 months prior to diagnostic liver biopsy, under the following conditions:~~ ~~• no change in dose for patients treated by GLP-1 agonists~~ ~~• no qualitative change up to Randomization (i.e., implementation of a new anti-diabetic therapy) for patients treated with metformin, gliptins, sulfamides, or insulin.~~ ~~.• no qualitative change up to 72 week of treatment (V7) (i.e., implementation of new drug) for patients treated with sodium/glucose cotransporter 2 (SGLT2) inhibitors~~.
Section 4.2 Exclusion criteria	1. Known **chronic** heart failure (Grade I to IV of New York Heart Association classification). 2. History of efficient bariatric surgery within 5 years prior to Screening**, or planned bariatric surgery in the course of the study**. 7. Patients with a history of clinically significant acute cardiac event within 6 months prior to Screening such as: ~~acute cardiovascular episode~~, stroke, transient ischemic attack, or coronary heart disease (angina pectoris, myocardial infarction, revascularization procedures). ~~11. Patients who have donated blood or blood products within 1 month prior to Screening or who plan to donate blood or blood products at any time during the trial and in the 2 months following the end of the study.~~ 12. Other well documented causes of chronic liver disease according to standard diagnostic procedures including, but not restricted to: o Positive hepatitis B surface antigen (HBsAg) o **Positive** HCV RNA**, (tested for in case of known cured HCV C infection, or positive HCV Ab at Screening)** o Suspicion of drug-induced liver disease o Alcoholic liver disease o Autoimmune hepatitis o Wilson's disease~~ hemochromatosis~~ o Primary biliary cirrhosis, primary sclerosing cholangitis

Section	**New Text**
	○ Genetic **homozygous** hemochromatosis ○ Known or suspected HCC ○ History or planned liver transplant, or current MELD score >12. 13. Where applicable, patients not covered by Health Insurance System and/or not in compliance with the recommendations of National Law in force **applicable to clinical Trials**. **18.** Fibrates are not permitted from 2 months before Randomization. Patients that used statins**,** ~~or~~ ezetimibe**, or nonfibrate lipid lowering drugs** before Screening may participate if the dosage has been kept constant for at least 2 months prior to Screening. **26.** ~~Total~~ **Conjugated** bilirubin >~~25 µmol/L (~~1.50 mg/dL~~)~~ **due to altered hepatic function. NOTE: Gilbert Disease patients are allowed into the study**. **27.** INR >1.4**0 due to altered hepatic function**. **28.** Platelet count <100,000/mm^3 **due to portal hypertension**.
Section 5.1.3 **Home pregnancy test for women of childbearing potential**	**Women of childbearing potential are required to perform a pregnancy test every 4 weeks. Home pregnancy test kits will be supplied at each visit to WOCBP and these are to be performed as per the kit instructions every 4 weeks between study visits. Negative results are to be reported at the next scheduled visit or telephone visit (see Table 1 and Figure 2). In the event of a positive result the patient must discontinue study drug immediately and report the result to the Investigator as soon as possible (see Section 8.6.1).**
Section 5.1.4. **Sun exposure**	**As a conservative approach patients will be advised to avoid extended ultra-violet light exposure without protection from V1 through to the end of the study (see Section 1.4.4.4).**
5.3. **Patient rescreening**	**Re-screening is allowed in a screen failed patient if there is a change in the situation of the patient which allows him/her to fulfill inclusion/exclusion criteria. This will need sponsor approval. In case of re-screening the patient will need to sign a new informed consent, will be entered as a new patient, with a new patient number.**

Section	**New Text**
6.1.2.2 Urinary pregnancy tests	Urinary pregnancy tests will be supplied to each site to perform a pregnancy diagnostic at each visit during the study on WOCBP. **These tests will also be given to the WOCBP to perform a pregnancy test at home every 4 weeks in between visits (see Section 5.1.3).**
6.1.4 Pharmacokinetic evaluation	Section removed and all text throughout relating to pharmacokinetic assessments/analysis removed. This will be addressed through a specific sub-study protocol.
Section 9 Statistical methods and data analysis	In all circumstances, a final SAP should be issued prior to database lock and treatment unblinding. The first approved version of the SAP should be available within 3 months of ~~protocol submission~~ **first patient randomized** and before the first DSMB meeting.
9.4.1 Resolution of NASH	The number and percentage of patients with resolution of NASH without worsening of fibrosis at the end of the 72 week treatment period will be summarized by treatment group. The main analysis will be performed using a logistic regression model, with fixed terms for treatment, type 2 diabetes (yes, no), gender (male, female), fibrosis stage (F2, F3) and baseline NAS. The statistical model will be used to calculate the odds ratio (elafibranor/placebo) and **99%** ~~95%~~ confidence interval. The main confirmatory analysis will be performed when ~~approximately 50% of patients (~~at least 1023~~)~~ **F2/F3** patients have completed the 72 week treatment period or discontinued from the study. The main analysis will be based on the ITT. Supportive analysis will be based on the PPS.
9.4.2 Long-term endpoints	The data will be analyzed using a Cox proportional hazards model with fixed terms for treatment, type 2 diabetes, gender, fibrosis stage, and baseline NAS. The Cox proportional hazards model will be used to calculate the hazard ratio (elafibranor/placebo) and **96%** ~~95%~~ confidence interval. This will be performed when at least 456 patients experience a clinical event/death. **The time to clinical event/death and time to first cardiovascular event death will also analyzed using an unadjusted Cox-proportional hazard's model, log rank test and a nonparametric randomization based analysis of covariance method proposed by Saville and Koch.[36]**

Section	**New Text**
Section 9.5.3 Subgroup analyses	• Race (Caucasian, ~~hispanic,~~ Other) • **Ethnicity (Hispanic, not Hispanic)** • Age (<~~55~~**60**, ≥~~55~~**60** years).
Section 9.6. Strategies to control type I error	~~The overall type I error for this study is two sided α=0.05. The alpha for the primary endpoints will be split 20%/80%, with two sided α=0.01 for resolution of NASH and two sided α=0.04 for time to clinical event/death.~~ The overall type I error for the primary endpoints in this study is two-sided α=0.05. The alpha for the primary endpoints will be split 20%/80%, with two-sided α=0.01 for resolution of NASH and two-sided α=0.04 for time to clinical event/death. A hierarchical gate-keeping strategy will be used to control for multiplicity for the key secondary endpoint. If the resolution of NASH without worsening of fibrosis endpoint is statistically significant, the key secondary endpoint, improvement of fibrosis according to NASH CRN scoring, will be tested in a confirmatory manner with a two-sided α=0.~~5~~**01**.
Section 9.9. ~~Blinded reassessment~~ **Interim analysis**	~~A blinded reassessment of the clinical event rate will be made when all patients have either completed or discontinued from the 72 week treatment period. The number of patients enrolled may be increased at this time and/or total duration extended. No adjustment will be made to the targeted number of events required for the final analysis of the long term endpoint, so no adjustment for control of type I error should be required for this reassessment.~~ **An adaptive design interim analysis will be performed after 140 primary events (approx. 30% of the 456 required events) have been accrued. The interim analysis will be performed by an unblinded team separate from the study team. The Data Safety Monitory Board (DSMB) will review the interim analysis results and provide final recommendations regarding trial termination due to futility and adjustment of the target number of primary events. Details will be in the DSMB Charter and SAP.**

<table>
<tr><th>Section</th><th>New Text</th></tr>
<tr><td>Appendix III:

Permitted/non-permitted medication</td><td>
Table II PERMITTED MEDICATION AND CONDITION
<table>
<tr><td>Medications</td><td>When</td></tr>
<tr><td colspan="2">Antidiabetic therapy</td></tr>
<tr><td>~~Conditions upon inclusion~~</td><td>-</td></tr>
<tr><td>GLP-1 agonist</td><td>Dose stability required in the 6 months prior to the ~~inclusion~~ diagnostic liver biopsy ~~up to EOT visit~~
No qualitative change (i.e., no initiation ~~implementation~~ of a new drug) from at least 6 months prior to the diagnostic liver biopsy up to 72-week of treatment (V7). Dose changes after randomization should be avoided.</td></tr>
<tr><td>All other ATD therapy (insulin, ~~sulfamides~~ sulfonylureas, metformin, gliptins), ~~SGLT2 inhibitors~~</td><td>No qualitative change (i.e., no ~~implementation~~ initiation of a new drug) from at least 6 months prior to the ~~inclusion~~ diagnostic liver biopsy and up to Randomization. ~~EOT visit~~ (Dose changes are allowed). Dose changes after randomization are allowed.</td></tr>
<tr><td>SGLT2-inhibitors</td><td>No qualitative change (i.e., no initiation of a new drug) from at least 6 months prior to the diagnostic liver biopsy up to 72-weeks of treatment (V7). Dose changes after randomization should be avoided.</td></tr>
<tr><td>~~Conditions during the study~~</td><td>-</td></tr>
<tr><td>~~GLP-1 agonist~~</td><td rowspan="2">~~Initiation of these therapies is prohibited during the study up to EOT Visit~~</td></tr>
<tr><td>~~Glitazones~~</td></tr>
<tr><td colspan="2">Lipid lowering therapy</td></tr>
<tr><td>Statins</td><td rowspan="3">Dose stability required from at least 2 months prior to Screening ~~up to EOT Visit.~~ Dose changes are allowed after Randomization if judged necessary by the physician</td></tr>
<tr><td>Ezetimibe</td></tr>
<tr><td>Other nonfibrate lipid lowering therapies</td></tr>
<tr><td colspan="2">Others</td></tr>
<tr><td>Vitamin E >400 IU/day</td><td rowspan="3">Dose stability required from at least 6 months prior to the ~~inclusion~~ diagnostic liver biopsy. ~~up to EOT Visit~~ Dose changes should be avoided up to EOT</td></tr>
<tr><td>PUFAs >2 g/day</td></tr>
<tr><td>Ursodeoxycholic acid</td></tr>
</table>
Abbreviations: ATD = autoimmune thyroid disease; EOT = end of study treatment; GLP-1 =glucagon-like peptide 1; PUFA = polyunsaturated fatty acids; SGLT2 = sodium/glucose cotransporter 2.
</td></tr>
</table>

Summary of minor changes to the protocol:

The following minor changes were made to the protocol:

- the version number and date were updated throughout the protocol
- typographical errors and formatting were corrected throughout the protocol
- abbreviation was added to the list of abbreviations for FITT
- amendment of study duration dates
- amendment of study contact details: amendment of study drug supplier contact information:

International Coordinating Investigator Committee	[redacted]
Medical Monitor	[redacted]
Project Director	[redacted]
~~Senior Project Manager~~ **IXRS**	[redacted]
Study drug supplier	[redacted]

- multiple minor editorial amendments for increased clarity and consistency including but not limited to the following:
    - "comorbidities" was amended to "conditions" throughout
    - "48 weekly" was amended to "every 48 weeks" throughout
    - "24 weekly" was amended to "every 24 weeks" throughout
    - "GFT505" was amended to "elafibranor" throughout
    - "box" amended to "carton" throughout
    - "interim analysis" amended to "surrogate endpoint analysis" where appropriate
    - eGFR was defined as being modification of diet in renal diseases (MDRD derived)
    - Objectives and endpoints were amended to include "120 mg" throughout
    - "Time to first occurrence" was amended to "the onset" throughout
    - "approximately 50% of the F2 and F3 patients" was amended to "1023 F2 and F3 patients" throughout
    - "Sulfamides" was amended to "sulfonylureas" throughout
- Table 1: STUDY GENERAL ASSESSMENT SCHEDULE

	Screening Period		
Visit	SV1	SV2 [5]	SPV [6]
Week	*-12 to -8*	*-12 to -4*	*-1* [6]
Permitted Margin			
Send sample for central histological evaluation of NASH diagnosis / change	X	**X**	

- Section 1.11. RATIONALE FOR SAFETY MONITORING

  Text updated to amend frequency of monitoring
- Section 1.4.1 Pharmacology

  Duplicate text deleted
- Section 1.5.1 Phase I program
- *Updated subject numbers for consistency with current Investigator's Brochure (Version 21)*Section 2.3. Other secondary objectives

  Wording updated to increase clarity
- Section 3.8.1 Long-term Treatment Period visits (V8 to Vn)
    - Study placebo or drug dispensation (described in Section 7.6)~~, with the exception of the final Vn visit)~~
- Section 4.1. Inclusion criteria

  Minor amendment to inclusion criteria 7 to ensure consistency with rest of protocol

  Minor amendment to inclusion criteria 8 to clarify the number of biopsies

  Minor amendment to inclusion criteria 9 to clarify requirements

- Section 4.2. Exclusion Criteria

  Minor changes to exclusion criteria 1, 5, 6, 12, 20, 26, and 30 to clarify requirements
- Section 5.1.1 Standard Diet and exercise recommendations

  Text deleted to remove specific wording for compliance question
- Section 6.1.1.1. Recommendations related to liver biopsy

  Note: Liver biopsy should be performed according to the good practices and local hospital standards, including the required exams prior to or on the day of the biopsy; Thus, the recommendations were simplified as below, to allow sites to follow their local requirements.

  Before performing a percutaneous liver biopsy, there must be a clearly defined indication for the biopsy, and the risks to the patient should not outweigh the potential benefits. **This will be assessed by the Investigator according to local practice.**

  ~~Patients who are about to undergo a percutaneous liver biopsy should have had some form of imaging of the liver within the preceding weeks. This will allow the detection of abnormal anatomy in the area of the proposed biopsy.~~

  In case the liver biopsy fragment is too small or of bad quality, thereby precluding adequate reading, other available slides or new slides to be prepared from an available block of tissue may be requested to the site.
- Section 6.1.2. Biological assessments

  Text amended for increased clarity of procedural requirements
- Section 6.1.2.3 Serology (SB1)

  Text amended for increased clarity of procedural requirements
- Section 6.2.1. Physical examination

  Text amended for increased clarity of procedural requirements.
- **Section 6.2.2. Waist circumference**

  Waist circumference will be measured at the midpoint between the lateral iliac crest and the lowest rib in cm during expiration. The measuring tape should be snug but not compressing the skin and held parallel to the floor. The measurement is to be made at normal respiration.
- Section 6.2.5 FibroScan

  Text updated for increased clarity of procedural requirements
- Section 6.3.1 Creatine phosphokinase

  Text amended for increased clarity of procedural requirements

- Section 6.3.2 Liver function monitoring

  In all cases, whether baseline AT values are normal or elevated, an increase of AT>10 x ULN will lead to permanent discontinuation of the patient from study drug, and scheduling of EOT visit (Section 3.9).
- Section 6.3.2.1 Monitoring of patients with normal baseline aminotransferase values

  Text amended for increased clarity of monitoring requirements
- Section 6.3.2.2 Monitoring of patients with increased baseline **aminotransferase** ~~AT~~ values

  Text amended for increased clarity of monitoring requirements
- Section 6.3.2.3 Monitoring of all patients

  Section deleted, text amended and moved to Section 6.3.2.1
- Section 6.3.3. Threshold for ~~diagnosisic~~ **diagnosis** of cirrhosis

  Text amended for increased clarity of procedural requirements
- Section 6.4. Safety **& efficacy** data review

  An independent DSMB will be established in order to review the progress of the study and to perform a safety data review on a regular basis during the trial to protect patient welfare and preserve study integrity. **The DSMB will also review the interim analysis results and provide final recommendations regarding trial termination due to futility and adjustment of the target number of primary events. A detailed description of the interim analysis procedures and decision-making process will be provided in the DSMB Charter.**

  The DSMB will consist of at least **5**~~4~~ experienced physicians (1 ~~each of~~ endocrinologist, **1** cardiologist, **1** hepatologist, **1 oncologist,** and **1** nephrologist) and 1 statistician, all of whom will be independent of the participants in the study. **The**~~A~~ DSMB Charter will define the role, responsibilities, rules, and tasks of the DSMB.
- Section 6.5. Clinical event committee

  The CEC will ~~specifically assess and adjudicate~~ **conduct adjudication of** all disease progression events included in the primary composite efficacy long-term endpoint (Section 1.9.2, except for histological cirrhosis), all DILI events, and all major cardiovascular ~~events: i.e., cardiovascular death, nonfatal myocardial infarction and stroke~~ events as defined in the CEC **charter**~~manual~~.

  The CEC will **be** comprise**d of** 2 hepatologists, ~~and 1~~ **2** cardiologist**s and 1 endocrinologist**, all of whom will be independent of the participants in the study.
- Section 6.6.1 summary of safety data

  Text updated for consistency with current Investigator's Brochure (Version 21).
- **Section 6.6.3 Benefit / risk assessment**

  Numerous Phase I and Phase IIa clinical studies have provided data that support the therapeutic potential of elafibranor in metabolic diseases including NASH. Moreover, the Phase IIb trial demonstrated the efficacy of elafibranor at the therapeutic dose of 120 mg on a clinically meaningful primary endpoint, resolution of histological NASH without worsening of fibrosis, in patients with active disease (NAS ≥4). While the trial

was short and not designed for antifibrotic endpoints, it nonetheless showed that elafibranor, at 120 mg daily, improved fibrosis indirectly through the resolution of NASH. Importantly, elafibranor 120 mg concomitantly improved the cardiometabolic risk profile of the patients by decreasing plasma triglycerides, total and LDL-cholesterol, increasing HDL-cholesterol, and improving inflammation, insulin resistance, and glucose homeostasis. Together these results position elafibranor as a drug candidate to treat NASH with the objective to block fibrosis evolution and ultimately avoid long term liver outcomes while reducing cardiovascular risk.

Moreover, clinical studies completed to date have not raised any major safety concerns associated with elafibranor treatment, thus providing a favorable efficacy/safety profile for the drug candidate.

Despite this favorable benefit-risk profile, an independent Data Safety Monitoring Board (DSMB) is to be established in order to review the safety of the treatment during the trial in an unblinded manner, to protect patient welfare and preserve study integrity. The safety assessments will be performed on a regular basis, every 6 months after Randomization of the first patient. The DSMB will consist of 5 experienced physicians (1 endocrinologist, 1 cardiologist, 1 hepatologist, 1 oncologist, and 1 nephrologist) and 1 statistician, all independent of the participants in the study.

In addition, throughout the study, patients will benefit from close safety monitoring including assessment of many safety parameters and follow-up of the disease progression, mainly through noninvasive measures including FibroScan.

- Section 7.2.2. Labeling
  Text amended to reflect updated regulations
- Section 7.11. TREATMENT ACCOUNTABILITY, RETRIEVAL AND DESTRUCTION
  Text amended for increased clarity
  Section 7.12.1. Handling of concomitant medication
  Text amended for increased clarity
- Section 7.12.2. Non-permitted medication (see Table I, APPENDIX III: Permitted/non-permitted medication)
  Text amended for increased clarity and to reflect updates in inclusion/exclusion criteria and Appendix III
- Section 7.12.3. Permitted medication under condition (see Table II, APPENDIX III: Permitted/non-permitted medication)
  Text amended for increased clarity and to reflect updates in inclusion/exclusion criteria and Appendix III
- Section 8.1.2. Serious adverse events
- In addition, any illnesses reported before starting active treatment or AE meeting the criteria of seriousness (as defined above) and considered to be possibly related (according to the

Investigator) to any study-specific procedure (e.g. ~~wash out period~~, laboratory testing procedure**, liver biopsy**) must be reported as an SAE.

- Section 8.1.2.2 Inpatient or prolonged hospitalization

  An inpatient hospitalization or prolongation of a hospitalization means that the patient stays overnight in the hospital. **An overnight stay is defined by hospitalization of 24 hours. Visits to the emergency room will not be considered hospital admission**.
- Section 8.1.3. Clarification on serious adverse events:
- **Events that are identified as primary efficacy endpoints for the long-term evaluation** ~~As an outcome event, progression to cirrhosis~~ should not be included as **an** AE.
- Section 8.3.1. Reporting an adverse event

  All AEs regardless of seriousness or relationship to study drug, including those occurring during the Screening Period, are to be recorded on the corresponding page(s) of the eCRF and in the patient's medical record from the ICF signature until **study end for each patient** ~~the last study visit~~.

  Adverse event reporting begins from signature of the patient ICF at the first Screening Visit and ends at **study end for each patient** ~~the last study visit~~.
- Section 8.3.2. Reporting a serious adverse event

  Serious AE reporting begins from signature of the patient ICF and ends at ~~the last study visit~~ **study end for each patient**.

  Any of the portal hypertension/cirrhosis related events described in Section 2.1.1 ~~Events~~ that are identified as potential **primary** efficacy endpoints for long-term evaluation will NOT be reported as SAEs unless it is determined by the adjudication committee that the event does not meet the predefined criteria for an endpoint. Events that are identified as potential **primary** efficacy endpoints for long-term evaluation that are not confirmed by adjudication will be reported as described with the start of the reporting time window being the time of negative adjudication decision.
- Section 8.6.1. Pregnancy

  Text amended to add requirement for pregnant female partners to sign informed consent for pregnancy reporting
- Section 9 Statistical methods and data analysis

  The first approved version of the SAP should be available within 3 months of ~~protocol submission~~ **first patient randomized** and before the first DSMB meeting.
- Section 9.2.2

  ~~To evaluate the efficacy of elafibranor 120 mg QD versus placebo on~~ **The long term endpoint of** clinical outcomes ~~described as~~ ~~**is**~~ a composite endpoint composed of death due to any cause, liver cirrhosis, and the full list of portal hypertension/cirrhosis related events

- Section 9.5.1. Key secondary endpoint

  The analysis will be performed at the time of the ~~interim analysis~~ **surrogate endpoint analysis** when ~~approximately 50% of patients (~~at least 1023~~)~~ **of patients with fibrosis stage F2 and F3** have completed the 72 week treatment period or discontinued from the study. **The null hypothesis will be tested at the two-sided 0.01 alpha level.**

- Section 9.5.2. Other secondary endpoints

  Continuous endpoints will be analyzed using an Analysis of Covariance (ANCOVA) model with fixed terms for treatment, type 2 diabetes, gender, fibrosis stage, and baseline NAS. An unstructured covariance matrix will be used for this analysis. The statistical model will be used to calculate the mean treatment difference and 95% confidence interval. If the data does not meet the required assumptions for parametric tests, the data will be analyzed using a nonparametric **analysis of covariance method of Koch et al.[37]** ~~Wilcoxon rank sum test. The median treatment difference and 95% confidence interval will be calculated using the Hodghes Lehmann method.~~

- Section 9.8 Safety Analysis

  Vital signs recorded at each timepoint and change from baseline will be summarized by treatment group using descriptive statistics. ~~The QTc and other ECG parameters recorded at each timepoint and change from baseline will also be summarized using descriptive statistics.~~

- Section 10.1. ~~CRF~~ Case report form and source documents

  Text amended for increased clarity

- Appendix V

  Text amended to remove site number from wallet

CLINICAL TRIAL SYNOPSIS

Sponsor:	Study Drug:	Protocol Number:
GENFIT	Elafibranor (GFT505): Propanoic acid, 2-[2,6-dimethyl-4-[3-[4-(methylthio)phenyl]-3-oxo-1(E)-propenyl] phenoxy]-2-methylpropanoic acid	GFT505-315-1

Title of the study:
A Multicenter, Randomized, Double-Blind, Placebo-Controlled Phase III Study to Evaluate the Efficacy and Safety of Elafibranor in Patients with Nonalcoholic Steatohepatitis (NASH) and fibrosis

Phase:
Phase III
Indication:
NASH

Study design and dose levels:
Randomized, double-blind, parallel groups (placebo or elafibranor [GFT505]) placebo-controlled study, evaluating the efficacy and safety of elafibranor 120 mg QD versus placebo in an adult NASH population with fibrosis. The first double-blind 72-week treatment period will assess the efficacy and safety of elafibranor on the resolution of NASH without worsening of fibrosis at the surrogate endpoint efficacy analysis, followed by a Long-term Treatment Period (LTTP) to assess efficacy on progression to cirrhosis, all-cause mortality, and liver-related clinical outcomes as measured by the onset of any of the listed adjudicated events.
Dose level
120 mg
Route of administration:
Oral (1 tablet once daily [QD])

Primary objectives – surrogate endpoint analysis
To evaluate the efficacy of elafibranor 120 mg QD for 72 weeks versus placebo on resolution of NASH without worsening of fibrosis.

- Resolution of NASH is defined as the disappearance of ballooning and disappearance or persistence of minimal lobular inflammation (grade 0 or 1) with an overall pattern of injury not qualifying for steatohepatitis.
- Worsening of fibrosis is evaluated using the NASH Clinical Research Network (CRN) fibrosis staging system and defined as progression of at least 1 stage.

Primary objectives – long-term endpoints
To evaluate the efficacy of elafibranor 120 mg QD versus placebo on clinical outcomes described as a composite endpoint composed of death due to any cause, liver cirrhosis, and the full list of portal hypertension/cirrhosis related events:

- Liver transplantation
- MELD score ≥15
- Hepatocellular carcinoma
- the onset of:
    - variceal bleed,
    - hepatic encephalopathy,
    - spontaneous bacterial peritonitis,
    - ascites,
    - hepatorenal syndrome,
    - hepatopulmonary syndrome,
    - chronic gastrointestinal blood loss due to portal hypertensive gastropathy (provided that these lead to hospitalization or transfusion).

Key secondary objective (at surrogate endpoint analysis)
To assess histological changes after 72 weeks of treatment on the following endpoint:

- Percentage of patients with improvement of fibrosis of at least 1 stage according to NASH CRN scoring.

Other secondary objectives

- To assess histological changes after 72 weeks of treatment and follow-up biopsy on the following endpoints:
  - percentage of patients with resolution of NASH without worsening of fibrosis (follow-up biopsy)
  - percentage of patients with improvement of fibrosis of at least 1 stage according to NASH CRN scoring
  - percentage of patients with at least 1 point improvement in histological scores (NASH CRN scoring: total nonalcoholic fatty liver disease (NAFLD) activity score (NAS), steatosis, hepatic ballooning, lobular inflammation), fibrosis (NAFLD Ishak scoring system), or portal inflammation
  - percentage of patients with improvement of NAS of at least 2 points.
  - percentage of patients with at least a 1 point improvement in steatosis-activity-fibrosis (SAF) activity score
  - mean changes in NAS, steatosis, hepatic ballooning, lobular inflammation, portal inflammation, SAF activity score
  - changes in area of fibrosis by morphometry
  - mean changes in fibrosis using NASH CRN and NAFLD Ishak scoring.
- To assess the following endpoints at Week 72, and at the end of the LTTP:
  - changes in liver enzymes and liver markers
  - changes in noninvasive markers of fibrosis and steatosis
  - changes in lipid parameters
  - variation in body weight
  - changes in insulin resistance and glucose homeostasis markers
  - changes in inflammatory markers
  - changes in cardiovascular risk profile as assessed by Framingham scores
  - changes in quality of life (36-Item Short-Form Health Survey [SF-36]) questionnaire)
- To assess the onset to:
  - liver cirrhosis
  - death of any cause
  - any portal hypertension or cirrhosis related events
  - cardiovascular events
  - liver-related death events.

Exploratory objectives

- To constitute a biobank for discovery and validation of biomarkers in NASH.

Exploratory objectives for F1 group

- To explore the following endpoints in F1 patients in the exploratory group at Week 72 and at the end of the LTTP:
  - resolution of NASH without worsening of fibrosis
  - percentage of patients with at least 1 point reduction in NASH CRN fibrosis score and NAFLD Ishak score
  - percentage of patients with at least 1 point improvement in NAS, steatosis, ballooning, lobular inflammation, or portal inflammation
  - percentage of patients with improvement of NAS of at least 2 points
  - percentage of patients with at least a 1 point improvement in SAF activity score
  - mean changes in NAS, fibrosis (using NASH CRN or NAFLD Ishak scoring system), steatosis, hepatic ballooning, lobular inflammation, portal inflammation, SAF activity score
  - changes in area of fibrosis by morphometry.
- To explore the following endpoints in F1 patients at Week 72 and after the LTTP:
  - composite long-term endpoints
  - cardiovascular events
  - changes in liver enzymes and liver markers
  - changes in noninvasive markers of fibrosis and steatosis
  - changes in lipid parameters
  - variation in body weight
  - changes in insulin resistance and glucose homeostasis markers
  - changes in inflammatory markers
  - changes in cardiovascular risk profile as assessed by Framingham scores

- changes in quality of life (SF-36 questionnaire).
- To assess the tolerability and safety.

Safety secondary objectives

- To assess the tolerability and safety of once a day administration of oral doses of elafibranor 120 mg:
  - serious adverse events, adverse events, physical examination, vital signs, medical history, electrocardiogram
  - hematological parameters
  - liver markers
  - renal biomarkers (including urinalysis)
  - cardiac biomarkers
  - metabolic parameters
  - other biochemical safety markers.

Patient population:

NASH diagnosed as:

Steatohepatitis evaluated by a centrally-read liver biopsy taken within 6 months prior to Screening (if no historical biopsy is available for NASH diagnosis, a liver biopsy will be performed during the Screening Period) with:

- At least a score of 1 in each component of the NAS (steatosis scored 0-3, ballooning degeneration scored 0-2, and lobular inflammation scored 0-3).
- NAS ≥4.
- fibrosis stage of 1 or greater and below 4, according to the NASH CRN fibrosis staging system.
  For patients with fibrosis stage 1, only patients at high risk of progression will be included, meaning with a NAS ≥5 and at least 2 of the following conditions: persistent elevated alanine aminotransferase (ALT; absence of normal value of ALT within the past year), obesity defined by a body mass index (BMI) ≥30, metabolic syndrome (NCEP ATP III definition), type 2 diabetes, or homeostasis model assessment of insulin resistance (HOMA-IR) >6.

At the end of the 72-week treatment period, patients will continue in the double-blind LTTP. Patients will be monitored by notably measuring the potential appearance of cirrhosis (based on FibroScan measurement for presence of cirrhosis associated with biological and clinical assessments). If histological cirrhosis is confirmed as well as any other event listed in the long-term composite endpoint, patients will be discontinued from study.

Number of estimated randomized F2-F3 Patients: total 2022 patients (ratio 2:1)

- 674 patients in placebo group
- 1348 patients in elafibranor (GFT505) group

An additional 202 (10% of the F2-F3 patients) F1 patients at high risk of progression will be included as an exploratory arm.

Number of participating centers (planned): ~250 centers

Number of participating countries: ~25 (Belgium, France, Germany, Italy, the Netherlands, Romania, Spain, UK, Switzerland, Portugal, Denmark, Finland, Sweden, Czech Republic, Russia, Turkey, USA, Canada, Mexico, Colombia, Brazil, Argentina, Chile, Australia, South Africa)

Study duration per patient:

Estimated duration approximately 72 months, based on 456 patients experiencing a long-term composite endpoint event.

Schedule:

- Screening Period: Week-12 to Week -1 prior to Randomization.
- First Treatment Period: Week 0 to Week 72: period of treatment with elafibranor (GFT505) or placebo for 72 weeks.
- Long-term Treatment Period: Week 72 to end of study: extension of treatment with elafibranor (GFT505) or placebo (until occurrence of prespecified number of events).

Inclusion criteria:

Patients must meet all of the following inclusion criteria to be eligible for enrollment in the trial:

1. Males or females aged from 18 to 75 years inclusive at first Screening Visit.
2. Must provide signed written informed consent and agree to comply with the study protocol.
3. Females participating in this study must be of nonchildbearing potential or using highly efficient contraception for the full duration of the study and for 1 month after the end of treatment, as described below:
   - Cessation of menses for at least 12 months due to ovarian failure,

- Surgical sterilization such as bilateral oopherectomy, hysterectomy, or medically documented ovarian failure
- If requested by local IRB regulations and/or National laws, sexual abstinence may be considered adequate (the reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient)
- Using a highly effective nonhormonal method of contraception (bilateral tubal occlusion, vasectomized partner, or intra-uterine device)
- -Double contraception with barrier AND highly effective hormonal method of contraception (oral, intravaginal, or transdermal combined estrogen and progestogen hormonal contraception associated with inhibition of ovulation; oral, injectable, or implantable progestogen-only hormonal contraception associated with inhibition of ovulation; or intrauterine hormone-releasing system). The hormonal contraception must be started at least 1 month prior to Randomization.

4. Histological confirmation of steatohepatitis on a diagnostic liver biopsy by central reading of the slides (biopsy obtained within 6 months prior to Screening or during the Screening Period) with at least 1 in each component of the NAS (steatosis scored 0-3, ballooning degeneration scored 0-2, and lobular inflammation scored 0-3).
5. NAS ≥4.
6. Fibrosis stage of 1 or greater and below 4, according to the NASH CRN fibrosis staging system.
   For patients with fibrosis stage 1, only patients at high risk of progression will be included meaning with a NAS ≥5 and at least 2 of the following conditions: persistent elevated ALT (absence of normal value of ALT within the past year), obesity defined by a BMI ≥30, metabolic syndrome (NCEP ATP III definition), type 2 diabetes, or HOMA-IR >6.
7. Patients in whom it is safe and practical to proceed with a liver biopsy, and who agree to have:
   - 1 liver biopsy during the Screening Period for diagnostic purpose (if no historical biopsy within 6 months before Screening is available)
   - 1 liver biopsy after 72-weeks of treatment for assessment of the treatment effects on NASH
   - a final liver biopsy after approximately 4 years of treatment (V13), unless a liver biopsy has already been performed within the past year
   - 1 liver biopsy performed only in the case of suspicion of cirrhosis (to have a histological confirmation).
8. If a patient is treated with 1 of the following drugs: vitamin E (>400 IU/day), polyunsaturated fatty acids (>2 g/day), or ursodeoxycholic acid; a stable dose from at least 6 months prior to diagnostic liver biopsy is required.
9. For patients with type 2 diabetes, glycemia must be controlled. If glycemia is controlled by antidiabetic drugs, change in anti-diabetic therapy must follow these requirements:
   - no qualitative change 6 months prior to diagnostic liver biopsy up to Randomization (i.e., implementation of a new anti-diabetic therapy) for patients treated with metformin, gliptins, sulfonylureas, sodium/glucose cotransporter (SGLT) 2 inhibitors, glucagon-like peptide (GLP)-1 agonists, or insulin. Dose changes of these medications are allowed in the 6 months prior to diagnostic liver biopsy, except for GLP-1 agonists, which must remain on stable dose in the 6 months prior to diagnostic liver biopsy.
   - no implementation of GLP-1 agonists and SGLT2 inhibitors up to 72 weeks of treatment (V7).

   Initiation of any other antidiabetic drugs is allowed after Randomization based on treating physicians' judgment, except for glitazones which are prohibited 6 months prior to diagnostic liver biopsy until the end of treatment.

Exclusion criteria:

Patients who meet any of the following criteria will be excluded from entering the study:

1. Known chronic heart failure (Grade I to IV of New York Heart Association classification).
2. History of efficient bariatric surgery within 5 years prior to Screening, or planned bariatric surgery in the course of the study.
3. Uncontrolled hypertension during the Screening Period despite optimal antihypertensive therapy.
4. Type 1 diabetes patients.
5. Patients with hemoglobin A1c [HbA1c] >9.0%. If abnormal at the first Screening Visit, the HbA1c measurement can be repeated at the latest 2 weeks prior to Randomization. A repeated abnormal HbA1c (HbA1c >9.0%) leads to exclusion.
6. Patients receiving thiazoledinediones (glitazones [pioglitazone, rosiglitazone]) unless the drug was discontinued at least 6 months before the diagnostic liver biopsy.

7. Patients with a history of clinically significant acute cardiac event within 6 months prior to Screening such as: stroke, transient ischemic attack, or coronary heart disease (angina pectoris, myocardial infarction, revascularization procedures).
8. Weight loss of more than 5% within 6 months prior to Randomization.
9. Compensated and decompensated cirrhosis (clinical and/or histological evidence of cirrhosis). Notably, NASH patients with fibrosis stage = 4 according to the NASH CRN fibrosis staging system are excluded.
10. Current or recent history (<5 years) of significant alcohol consumption. For men, significant consumption is typically defined as higher than 30 g pure alcohol per day. For women, it is typically defined as higher than 20 g pure alcohol per day.
11. Pregnant or lactating females or females planning to become pregnant during the study period.
12. Other well documented causes of chronic liver disease according to standard diagnostic procedures including, but not restricted to:
    - positive hepatitis B surface antigen
    - positive hepatitis C Virus (HCV) RNA (tested for in case of known cured HCV infection or positive HCV Ab at Screening)
    - suspicion of drug-induced liver disease
    - alcoholic liver disease
    - autoimmune hepatitis
    - Wilson's disease
    - primary biliary cirrhosis, primary sclerosing cholangitis
    - genetic homozygous hemochromatosis
    - known or suspected hepatocellular carcinoma (HCC)
    - history or planned liver transplant, or current MELD score >12
13. Where applicable, patients not covered by Health Insurance System and/or not in compliance with the recommendations of National Law in force applicable to clinical trials.
14. Patients who cannot be contacted in case of emergency.
15. Known hypersensitivity to the investigation product or any of its formulation excipients.
16. Patients with previous exposure to elafibranor.
17. Patients who are currently participating in, plan to participate in, or have participated in an investigational drug trial or medical device trial containing active substance within 30 days or five half-lives, whichever is longer, prior to Screening.

Concomitant medications:

18. Fibrates are not permitted from 2 months before Randomization. Patients that used statins, ezetimibe, or other nonfibrate lipid lowering drugs before Screening may participate if the dosage has been kept constant for at least 2 months prior to Screening.
19. Currently taking drugs that can induce steatosis/steatohepatitis including, but not restricted to: corticosteroids (parenteral & oral chronic administration only), amiodarone (Cordarone), tamoxifen (Nolvadex), and methotrexate (Rheumatrex, Trexall), which are not permitted 30 days prior to Screening and up to end of treatment.
20. Currently taking any medication that could interfere with study medication absorption, distribution, metabolism, or excretion or could lead to induction or inhibition of microsomal enzymes, e.g., indomethacin, which are not permitted from Randomization until end of treatment.

Associated illnesses or conditions:

21. Any medical conditions that may diminish life expectancy to less than 2 years including known cancers.
22. Evidence of any other unstable or, untreated clinically significant immunological, endocrine, hematological, gastrointestinal, neurological, neoplastic, or psychiatric disease
23. Mental instability or incompetence, such that the validity of informed consent or ability to be compliant with the study is uncertain.

In addition to the above criteria, patient should not present any of the following biological exclusion criteria:

24. Positive anti-human immunodeficiency virus antibody.
25. Aspartate aminotransferase (AST) and/or ALT >10 x upper limit of normal (ULN).
26. Conjugated bilirubin > 1.50mg/dL due to altered hepatic function **Note**: Gilbert Disease patients are allowed into the study.
27. International normalized ratio >1.40 due to altered hepatic function.
28. Platelet count <100,000/mm^3 due to portal hypertension.

29. Serum creatinine levels >1.53 mg/dL in males and >1.24 mg/dL in females.
30. Significant renal disease, including nephritic syndrome, chronic kidney disease (defined as patients with markers of kidney damage or estimated glomerular filtration rate [eGFR] of less than 60 ml/min/1.73 m^2).
31. Unexplained serum creatine phosphokinase (CPK) >3 x the ULN. In case of explained elevated CPK >3 x the ULN, the measurement can be repeated prior to Randomization. In this case, retest should be performed within 1 to 2 weeks after initial test. A CPK retest >3 x ULN leads to exclusion.

Criteria for Evaluation:

Primary endpoint

Surrogate endpoint - resolution of NASH (at surrogate endpoint analysis)

To evaluate the efficacy of elafibranor 120 mg versus placebo on the resolution of NASH without worsening of fibrosis after 72 weeks of treatment.

Long-term endpoint – clinical outcomes (at final analysis)

To evaluate the efficacy of elafibranor 120 mg QD versus placebo on clinical outcomes described as a composite endpoint composed of death due to any cause, liver cirrhosis, and the full list of portal hypertension/cirrhosis related events:

- liver transplantation
- MELD score ≥15
- HCC
- the onset of:
    - variceal bleed
    - hepatic encephalopathy
    - spontaneous bacterial peritonitis
    - ascites
    - hepatorenal syndrome
    - hepatopulmonary syndrome
    - chronic gastrointestinal blood loss due to portal hypertensive gastropathy (provided that these lead to hospitalization or transfusion).

The final analysis will be performed when 456 patients experience an event listed above. This is expected to occur approximately 72 months after the first patient is randomized.

Key secondary endpoint (at surrogate endpoint analysis)

Percentage of patients with improvement of fibrosis of at least 1 stage according to NASH CRN scoring at 72 weeks.

Other secondary endpoints

- To assess histological changes after 72 weeks of treatment and follow-up biopsy on the following parameters:
    - percentage of patients with resolution of NASH without worsening of fibrosis (follow-up biopsy)
    - percentage of patients with improvement of fibrosis of at least 1 stage according to NASH CRN scoring
    - percentage of patients with at least 1 point improvement in histological scores (NASH CRN scoring: total NAS, steatosis, hepatic ballooning, lobular inflammation), fibrosis (NAFLD Ishak scoring system), or portal inflammation
    - percentage of patients improvement of NAS of at least 2 points
    - percentage of patients with at least a 1 point improvement in SAF activity score
    - mean changes in NAS, steatosis, hepatic ballooning, lobular inflammation, portal inflammation, SAF activity score
    - changes in area of fibrosis by morphometry
    - mean changes in fibrosis using NASH CRN and NAFLD Ishak scoring.
- To assess the following endpoints at Week 72, and at the end of the LTTP:
    - changes in liver enzymes and liver markers
    - changes in noninvasive markers of fibrosis and steatosis
    - changes in lipid parameters
    - variation in body weight
    - changes in insulin resistance and glucose homeostasis markers
    - changes in inflammatory markers
    - changes in cardiovascular risk profile as assessed by Framingham scores

  - changes in quality of life (SF-36 questionnaire).
- To assess the onset of:
  - liver cirrhosis
  - death of any cause
  - any portal hypertension or cirrhosis related events
  - cardiovascular events
  - liver-related death events.

Exploratory endpoints

- To constitute a biobank for discovery and validation of biomarkers in NASH.

Study Duration (planned): estimated 72 months (First Patient First Visit [FPFV]-Last patient last visit [LPLV])

- Regulatory/ethics committee submission: January 2016
- Initiation visits: March 2016 – March 2017
- Recruitment period: March 2016 – March 2018
- FPFV: March 2016
- Surrogate endpoint analysis: Q4 2018 – Q1 2019
- LPLV (LTTP): March 2022

Data Safety Monitoring Board (DSMB)

An independent DSMB will be established in order to review the progress of the study and to perform a safety data review on a regular basis during the trial to protect patient welfare and preserve study integrity. The DSMB will also review the interim analysis results and provide final recommendations regarding trial termination due to futility and adjustment of the target number of primary events.

The DSMB will consist of at least 5 experienced physicians (1 endocrinologist, cardiologist, hepatologist, oncologist, and nephrologist) and 1 statistician, all of whom will be independent of the participants in the study. The DSMB Charter will define the role, responsibilities, rules, and tasks of the DSMB.

Clinical events committee (CEC)

The CEC will conduct the adjudication of all disease progression events included in the primary composite efficacy long-term endpoint (except for histological cirrhosis), all drug-induced liver injury events, and all major cardiovascular events as defined in the CEC charter. The CEC assessment and adjudication will occur in a blinded, consistent, and unbiased manner throughout the course of a study to determine whether the endpoints meet the protocol-specified criteria.

The CEC will be comprised of 2 hepatologists, 2 cardiologists, and 1 endocrinologist all of whom will be independent of the participants in the study.

Table 1: STUDY GENERAL ASSESSMENT SCHEDULE

	Screening Period			First Treatment Period							Long-term Treatment Period		End Of Study Treatment
Visit	**SV1**	**SV2** [4]	**SPV** [5]	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**Phone Visit PV1-PVn**	**V8-Vn**	**EOT** [13]
Week	*-12 to -8*	*-12 to -4*	*-1* [5]	*0* [6]	*12* [6]	*24* [6]	*36* [6]	*48* [6]	*60* [6]	*72* [6]	*(every 24 weeks starting 12 weeks after V7)* [8]	*(every 24 weeks starting after V7)* [9]	*30 days after final study drug administration*
Permitted Margin				**0**	**± 1 week after V1**	**± 1 week after V1**	**± 1 week after V1**	**± 1 week after V1**	**± 1 week after V1**	**± 1 week after V1**	**± 2 weeks Compared to V7**	**± 2 weeks Compared to V7**	**± 1 week after last administration**
Obtain informed consent	X												
Medical history / demographics	X												
Check inclusion / exclusion criteria	X			X [7]									
Adequate diet and lifestyle recommendations, including alcohol restrictions and smoking habits	X – – –	– – –	– – –	– – –	– – –	– – –	– – –	– – –	– – –	– – –	– – –	– – – →	
Confirmation of diet and lifestyle compliance, including alcohol restrictions and smoking habits				X	X	X	X	X	X	X	X	X	X
Physical examination	X			X	X	X	X	X	X	X		X	X
Vital signs & height [1] **& weight measurement**	X			X	X	X	X	X	X	X		X	X
Waist circumference	X			X		X		X		X		X	X

	Screening Period			First Treatment Period							Long-term Treatment Period		End Of Study Treatment
Visit	**SV1**	**SV2** [4]	**SPV** [5]	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**Phone Visit PV1-PVn**	**V8-Vn**	**EOT** [13]
Week	*-12 to -8*	*-12 to -4*	*-1* [5]	*0* [6]	*12* [6]	*24* [6]	*36* [6]	*48* [6]	*60* [6]	*72* [6]	*(every 24 weeks starting 12 weeks after V7)* [8]	*(every 24 weeks starting after V7)* [9]	*30 days after final study drug administration*
Permitted Margin				**0**	**±1 week after V1**	**± 1 week after V1**	**± 1 week after V1**	**± 1 week after V1**	**± 1 week after V1**	**± 1 week after V1**	**± 2 weeks Compared to V7**	**± 2 weeks Compared to V7**	**± 1 week after last administration**
12-Lead ECG				X			X			X		X [10]	X
Lab evaluation (see Table 2)	X	X		X	X	X	X	X	X	X		X	X
Send sample for central histological evaluation of NASH diagnosis / change	X	X								X		X [11]	
Liver biopsy		X [4]								X		X [11]	
Phone call to patient to confirm eligibility of histology criteria			X [5]										
FibroScan [2]				X						X		X	
Contact the patient prior to visit [3]				X	X	X	X	X	X	X		X	X
Randomization				X									
IXRS registration	X			X	X	X	X	X	X	X	X	X	X
Review prior / concomitant medication	X			X	X	X	X	X	X	X	X	X	X
Quality of life assessment				X		X		X		X		X [12]	X

	Screening Period			First Treatment Period							Long-term Treatment Period		End Of Study Treatment
Visit	**SV1**	**SV2** [4]	**SPV** [5]	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**Phone Visit PV1-PVn**	**V8-Vn**	**EOT** [13]
Week	*-12 to -8*	*-12 to -4*	*-1* [5]	*0* [6]	*12* [6]	*24* [6]	*36* [6]	*48* [6]	*60* [6]	*72* [6]	*(every 24 weeks starting 12 weeks after V7)* [8]	*(every 24 weeks starting after V7)* [9]	*30 days after final study drug administration*
Permitted Margin				**0**	**±1 week after V1**	**± 1 week after V1**	**± 1 week after V1**	**± 1 week after V1**	**± 1 week after V1**	**± 1 week after V1**	**± 2 weeks Compared to V7**	**± 2 weeks Compared to V7**	**± 1 week after last administration**
Adverse events	X	X		X	X	X	X	X	X	X	X	X	X
Data collection on clinical outcomes					X	X	X	X	X	X	X	X	X
Study placebo or drug dispensation				X	X	X	X	X	X	X		X	
Drug accountability					X	X	X	X	X	X	X	X	X

Abbreviations: ECG = electrocardiogram; EOT = end of treatment; IXRS = Interactive voice/web Response System; LTTP = Long-term Treatment Period; NASH = nonalcoholic steatohepatitis; PV = phone visit; QOL = quality of life; SV = Screening visit; V = visit

1. Height is measured only at visit SV1.
2. Where possible FibroScan must be done at the day of visit. Otherwise, it can be performed within 7 days around the visit date.
3. During the study, the patient should be contacted at least 1 week before the next visit as a reminder on procedures and IP return.
4. This visit only occurs if no historical biopsy within 6 months before the Screening Visit is available. A screening liver biopsy and slides shipment to the central anatomopathologist must be performed at least 4 weeks before Randomization (in order to obtain the results in time). Coagulation (platelet count and PT [INR]) should be checked locally prior to this liver biopsy (according to local medical standards in each hospital).
5. Screening Phone Visit. Telephone contact for all patients at least 1 week before V1. Patients should be contacted regarding eligibility confirmation within 1 week prior to Randomization Visit V1. In case of ineligibility, the patient should be contacted as soon as possible.
6. The maximum time period between visits in the First Treatment Period is to be 96 days due to the study drug supply provided to the patient.
7. Check of all inclusion/exclusion criteria, including biological and histological criteria assessed at SV1 and SV2.

8. Phone visits every 24 weeks starting 12 weeks after V7 for safety, data collection on clinical outcomes, and IP compliance control. If any information during this phone contact requires a visit, the Investigator may decide to perform an unscheduled visit. Phone visits may also be performed at the same frequency for the follow-up of patients having permanently discontinued study drug but remaining in the study (Same information collected except IP compliance control).

9. The maximum time period between visits in the Long-term Treatment Period (LTTP) is to be 192 days due to the study drug supply provided to the patient.

10. In the LTTP the first ECG will be performed at V9 and then every 48.

11. Liver biopsy will be performed after approximately 4 years of treatment (V13) and in the case of suspicion of cirrhosis (based on FibroScan and/or clinical or biological assessment). In the case that the suspicion of cirrhosis is not confirmed by liver biopsy the patient shall remain on the study and a liver biopsy will be performed after approximately 4 years of treatment (V13, unless a biopsy has already been performed within the year). Blood sampling (coagulation tests; see Table 2) are to be performed locally before the biopsy.

12. QOL assessment questionnaire to be completed at 24 (V8), 48 (V9), and 96 (V11) weeks in the LTTP (following approximately 96, 120, and 168 weeks of treatment, respectively), and every 48 weeks thereafter.

13. EOT Visit to be performed 30 days after final study drug administration at the end of study or for any premature discontinuation (permanent study drug discontinuation or trial discontinuation).

Table 2: STUDY BIOLOGICAL ASSESSMENT SCHEDULE

Visit	Screening Period		First Treatment Period							Long-term Treatment Period	End of Study Treatment
	SV1 SB1 [6]	SB2 [7]	V1 B1	V2 B2	V3 B3	V4 B4	V5 B5	V6 B6	V7 B7	V8 to Vn B8 to Bn	EOT
Week	*-12 to -8*	*Prior to -4*	*0*	*12*	*24*	*36*	*48*	*60*	*72*	*Every 24 weeks*	*30 days after final study drug administration*
Hematology *Hemoglobin, hematocrit, RBC, WBC, differential count, platelet count, reticulocytes count, and PT (INR)*	X		X	X	X	X	X	X	X	X	X
Coagulation - local lab testing prior to liver biopsy *Platelet count, PT (INR)*[1]		X							X	X [1]	
Serology *HIV ab I/II, HBsAg, and HCV Ab (positive HCV RNA in case HCV Ab >0 or known cured hepatitis C infection*[2]*)*	X										
Screening Visit 1 - chemistry panel *HbA1c*[2]*, fasting plasma glucose, insulin (fasting), HOMA-IR creatinine, eGFR, GGT, AST, ALT, CPK*[2]*, alkaline phosphatase, total and conjugated bilirubin, sodium, TG, and MELD score*	X										
V1 to Vn total chemistry panel *HbA1c, fasting plasma glucose, creatinine, eGFR, GGT, AST, ALT, CPK, alkaline phosphatase, total proteins, albumin, electrolytes (sodium, potassium, chloride, calcium), uric acid, urea (BUN), total and conjugated bilirubin, hsCRP, total cholesterol, nonHDL-C, HDL-C, TG, calculated VLDL-C, ApoAI, ApoB, calculated LDL-C, and MELD score*			X [6]	X	X	X	X	X	X	X	X

Visit	Screening Period		First Treatment Period							Long-term Treatment Period	End of Study Treatment
	SV1 SB1 [6]	SB2 [7]	V1 B1	V2 B2	V3 B3	V4 B4	V5 B5	V6 B6	V7 B7	V8 to Vn B8 to Bn	EOT
Week	*-12 to -8*	*Prior to -4*	*0*	*12*	*24*	*36*	*48*	*60*	*72*	*Every 24 weeks*	*30 days after final study drug administration*
Urinalysis *albumin, creatinine, ACR, and microscopic analysis α1 microglobulin*, β-NAG,* N-Gal*, IL-18*, KIM-1*,*			X	X	X	X	X	X	X	X	X
Urinalysis (dipstick) *Specific gravity, pH, protein, glucose, ketones, bilirubin, urobilinogen, blood, nitrite, and leukocytes*	X		X	X	X	X	X	X	X	X	X
Urinary pregnancy tests [3]	X		X	X	X	X	X	X	X	X	X
Inflammatory markers *Fibrinogen, and haptoglobin*			X		X		X		X	X	X
Other Liver markers *CK18 (M65 & M30), adiponectin, ferritin, FGF19 & FGF21, alpha2 macroglobulin, hyaluronic acid, PIIINP, TIMP-1, and CHI3L1* [4]			* [4]		*		*		* [4]	* [4]	*
Calculated fibrosis & steatosis index *Fibrotest, ELF, NAFLD Fibrosis score, Steatotest, FLI, Fibrometre S, and FIB-4*			*		*		*		*	*	*
Other safety markers *Homocysteine, NT-ProBNP, troponin-T, and cystatin C*			*		*		*		*	*	*
Special glycemic and other lipid parameters *Insulin(fasting), HOMA-IR, Fructosamine, C-peptide, FFA, small dense LDL, ApoAII, Apo CIII, and Apo E*			*		*		*		*	*	*

Visit	Screening Period		First Treatment Period							Long-term Treatment Period	End of Study Treatment
	SV1 SB1 [6]	SB2 [7]	V1 B1	V2 B2	V3 B3	V4 B4	V5 B5	V6 B6	V7 B7	V8 to Vn B8 to Bn	EOT
Week	*-12 to -8*	*Prior to -4*	*0*	*12*	*24*	*36*	*48*	*60*	*72*	*Every 24 weeks*	*30 days after final study drug administration*
Sampling for additional parameters *Whole blood* [5]*, plasma, and serum bank*	* [5]		*	*	*	*	*	*	*	*	*

X = results available within 2 working days (routine analysis) * = batch analysis

Abbreviations Ab = antibody; ACR = albumin–creatinine ratio; Ag = antigen; ALT = alanine aminotransferase; Apo = apolipoprotein; AST = aspartate aminotransferase; β-NAG = N-acetyl-β-D-glucosaminidase; BUN = blood urea nitrogen; B = biological assessment Visit; CHI3L1 = chitinase-3-like protein 1; CK18 = cytokeratin 18; CPK = creatine phosphokinase; eGFR = estimated glomerular filtration rate; ELF = enhanced liver fibrosis; EOT = end of study treatment; FFA = free fatty acid; FGF = fibroblast growth factor; FIB-4 = fibrosis 4 score; FLI = fatty liver index; GGT = gamma-glutamyl transferase; HbA1c = hemoglobin A1c; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HDL-C = high density lipoprotein-C; HIV = human immunodeficiency virus; HOMA-IR = homeostasis model assessment of insulin resistance; hsCRP = high-sensitivity C-reactive protein; IL-18 = interleukin 18; INR = international normalized ratio; KIM-1 = kidney injury molecule-1; LDL-c = low density lipoprotein-C; MDRD = modification of diet in renal disease; MELD = model end stage liver disease; NAFLD = nonalcoholic fatty liver disease; N-Gal = neutrophil gelatinase-associated lipocalin; NT-ProBNP = N-terminal of the prohormone brain natriuretic peptide; PIIINP = type III procollagen peptide; PT = prothrombin time; TIMP-1 = tissue inhibitors of metalloproteinases 1; RBC = red blood cell; SB = Screening biological assessment Visit; SV = Screening Visit; TG = triglyceride; VLDL-C = very low density lipoprotein-C; V = Visit; WBC = white blood cell.

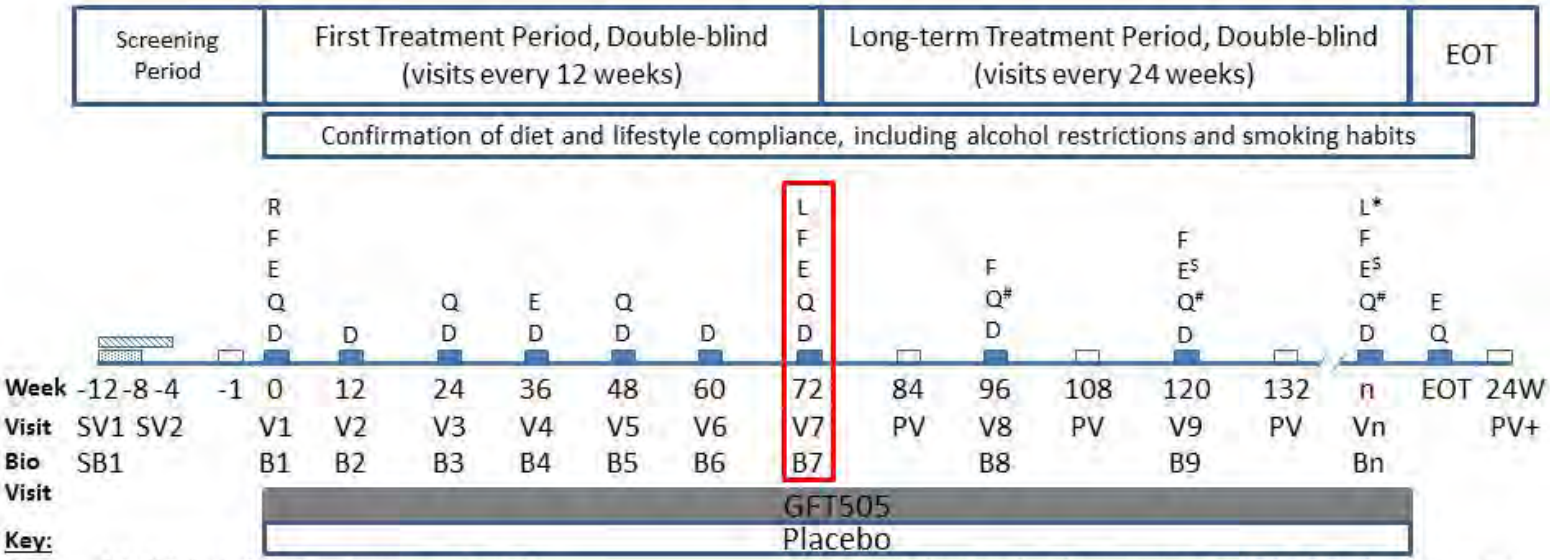
1. Coagulation (platelet count and PT [INR]) should be checked prior to any liver biopsy (according to local medical standards in each hospital). To be done through a local laboratory. Liver biopsy will be performed after 72 weeks (V7) and after approximately 4 years of treatment (V13) and in the case of suspicion of cirrhosis (based on FibroScan and/or clinical or biological assessment). In the case that the suspicion of cirrhosis is not confirmed by liver biopsy the patient shall remain on the study and a liver biopsy will be performed after approximately 4 years of treatment ([V13] unless a biopsy has already been performed within the past year).
2. Upon receipt of the results of the biological assessment performed at SV1, retesting or additional testing may be needed during the Screening Period:
   - CPK can be repeated prior to Randomization (V1) within 1 to 2 weeks after initial test.
   - HbA1c can be repeated prior to Randomization (V1), at the latest 2 weeks prior to planned Randomization.
   - HCV RNA can be tested, at SV1 in case of known cured hepatitis c infection, or in case of positive HCV Ab at SV1, at a retest screening visit at the latest 2 weeks prior to the planned Randomization (V1).
3. Dipstick at site for WOCBP only. In addition, home pregnancy tests are to be performed by WOCBP every 4 weeks from V1 (see Table 1 and Figure 2).
4. CHI3L1 to be tested only at V1, V7, and at the time of 4 years biopsy (V13).

5. Whole blood sample will be only taken at SV1 while plasma and serum samples are to be taken at every visit **ONLY** for patients who have signed the pharmacogenomic and biomarker ICF.

6. Visits SV1 and V1 should be scheduled at least 8 weeks apart in order to have 2 consecutive baseline values of AST, ALT, total bilirubin, and INR for DILI adjudication.

7. SB2, additional visit in the Screening Period if required for coagulation prior to liver biopsy.

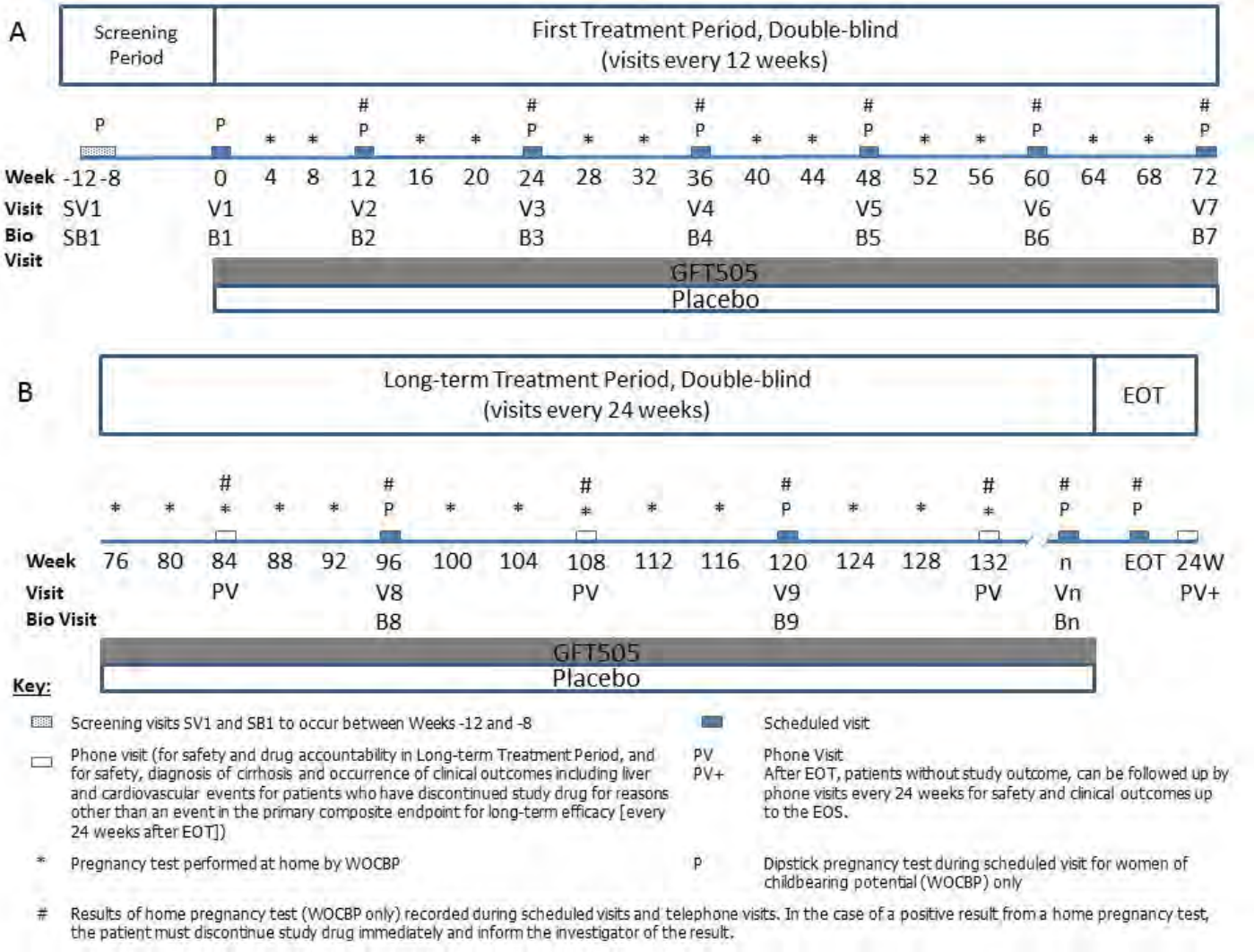
Figure 1: STUDY DURATION AND VISIT SCHEDULE



Key:

Bio Visit	Scheduled visits for biological assessment sampling	D	Study placebo or drug dispensation. No study placebo or drug dispensation will occur on the final Vn visit during the Long-term Treatment Period.
E	Electrocardiogram (ECG)	EOS	End of study
EOT	End of study treatment visit performed 30 days after final study drug administration at the end of study or for any premature discontinuation (permanent study drug discontinuation or trial discontinuation)	PV PV+	PV for safety, data collection of clinical outcomes, home pregnancy test results, and IP compliance control After EOT, patients without study outcome, can be followed up by phone visits every 24 weeks for safety and clinical outcomes up to the EOS.
L	Liver biopsy	F	FibroScan
Q	Quality of Life questionnaire	R	Randomization
S	Screening		Visit including clinical and laboratory evaluations
	Potential SV2 and SB2 visits for liver biopsy (if no historical biopsy 6 months prior to Visit 1)		Phone visit (for confirmation of eligibility in Week -1, for safety and drug accountability in Long-term Treatment Period, and for safety, diagnosis of cirrhosis and occurrence of clinical outcomes including liver and cardiovascular events for patients who have discontinued study drug for reasons other than an event in the primary composite endpoint for long-term efficacy [every 24 weeks after EOT])
	Screening visits SV1 and SB1 to occur between Weeks -12 and -8		
#	Quality of life questionnaire in Long-term Treatment Period performed at Visits V8, V9, and V11, and every 48 weeks thereafter	$	ECG performed every 48 weeks starting at visit V9
	Surrogate endpoint analysis performed and filed for initial market approval under Subpart H	*	Liver biopsy performed at approximately 4 years (visit V13) and in the case of suspicion of cirrhosis

Figure 2: PREGNANCY TESTING SCHEDULE FOR WOMEN OF CHILDBEARING POTENTIAL



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AASLD	American Association for the Study of Liver Diseases
ACR	albumin–creatinine ratio
ADR	adverse drug reaction
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	Analysis of Covariance
ApoAI	apolipoprotein AI
ApoAII	apolipoprotein AII
ApoB	apolipoprotein B
ApoCIII	apolipoprotein CIII
AST	aspartate aminotransferase
AT	aminotransferase
ATP	Adult Treatment Panel
BMI	body mass index
BP	blood pressure
BUN	blood urea nitrogen
Bx	biological assessment visit
CA	competent authorities
CEC	Clinical Events Committee
CFR	Code of Federal Regulations
CPK	creatine phosphokinase
CRN	Clinical Research Network
CRO	Clinical Research Organization
CRP	C-reactive protein
CSR	Clinical Study Report
CYP	cytochrome P450
DDI	drug-drug interaction
DILI	drug-induced liver injury
DSMB	Data Safety Monitoring Board
EASL	European Association for the Study of the Liver
ECG	electrocardiogram
eCRF	electronic case report form
EES	efficacy evaluable sample
eGFR	estimated glomerular filtration rate
EOS	end of study
EOT	end of study treatment
FDA	Food and Drug Administration
FFA	free fatty acid
FIB-4	fibrosis 4 score
FITT	full intent-to-treat set
FLI	fatty liver index
FPFV	first patient first visit
FSS	full safety set
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase

GLP1	glucagon-like peptide 1
HbA1c	hemoglobin A1c
HBsAg	hepatitis B surface antigen
HCC	hepatocellular carcinoma
HCV	hepatitis C Virus
HDL-C	High-density lipoprotein cholesterol
HIV	human immunodeficiency virus
HOMA-IR	homeostasis model assessment of insulin resistance
hPPAR	human peroxisome proliferator-activated receptor
HRT	Hormonal replacement therapy
HSC	hepatic stellate cells
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
INR	international normalized ratio
IP	investigational product
IR	insulin resistance
IRB	Institutional Review Board
ITT	intent-to-treat
IXRS	Interactive Voice/Web Response System
LDL-C	Low-density lipoprotein cholesterol
LPLV	last patient last visit
[redacted]	[redacted]
LTTP	Long-term Treatment Period
M2	anti-inflammatory macrophages
MedDRA	Medical Dictionary for Regulatory Activities
MELD	model end stage liver disease
NAFLD	nonalcoholic fatty liver disease
NAS	NAFLD Activity Score
NASH	nonalcoholic steatohepatitis
NCEP ATP III	National Cholesterol Education Program's Adult Treatment Panel III
PD	pharmacodynamics
PK	pharmacokinetics
PPAR	peroxisome proliferator-activated receptor
PPS	per protocol set
PT	prothrombin time
PUFA	polyunsaturated fatty acids
QD	once daily
QTc	corrected QT
SADR	serious adverse drug reaction
SAE	serious adverse event
SAF	steatosis, activity, and fibrosis
SAP	Statistical Analysis Plan
SBx	screening biological assessment visit
SF-36	36-Item Short-Form Health Survey
SGLT2	sodium/glucose cotransporter 2
SOP	Standard Operating Procedure

SS	safety set
SUSAR	suspected unexpected serious adverse reactions
SVx	Screening Visit x
TLC	therapeutic lifestyle change
TNFα	Tumor Necrosis Factor-alpha
ULN	upper limit of normal
UV-LLNA	UV- Local Lymph Node Assay
Vx	Visit x
WOCBP	women of childbearing potential

1. INTRODUCTION

1.1. NONALCOHOLIC STEATOHEPATITIS

Nonalcoholic fatty liver disease (NAFLD) is a spectrum of disorders characterized by excessive fat accumulation in the liver (steatosis). Nonalcoholic steatohepatitis (NASH) defines a subgroup of NAFLD where steatosis coexists with hepatocyte injury and inflammation (steatohepatitis), with or without fibrosis.

Nonalcoholic steatohepatitis is considered by the European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Diseases (AASLD) as an increasing public health issue owing to its close epidemiological association with the worldwide epidemic of obesity and type 2 diabetes.

The prevalence of NAFLD in the general population assessed by ultrasonography is 20% to 30% in Europe. A similar prevalence of 15% to 25% was documented histologically by postmortem studies. A high prevalence of histological NAFLD has been described in apparently healthy liver donors: 12% to 18% in Europe and 27% to 38% in the US. Furthermore, with a sensitive technique such as magnetic resonance spectroscopy, 34% have NAFLD.

Interestingly, 39% of newly diagnosed cases of chronic liver disease had NAFLD, making NASH one of the top causes of liver diseases in Western countries. Using the histological definition of NASH, recent studies have shown a high prevalence of NASH among NAFLD cases: 43% to 55% in patients with increased aminotransferases (ATs), 49% in morbidly obese patients, and 67% in a subset of patients with incident chronic liver disease. Finally, in apparently healthy liver donors the prevalence of NASH ranges from 3% to 16% in Europe and from 6% to 15% in the US.

The commonest cause of NASH is primary NAFLD-associated insulin resistance and its phenotypic manifestations, namely excess weight/obesity, visceral obesity, type 2 diabetes, hypertriglyceridemia, and arterial hypertension. A causal association has been suggested by longitudinal studies showing a chronological association between the progression of insulin resistance, the metabolic syndrome, and the occurrence of NAFLD/NASH.

1.2. PATHOPHYSIOLOGICAL PROCESS OF NONALCOHOLIC STEATOHEPATITIS

A widely described model suggests that the development of NAFLD into NASH requires several 'hits' or insults.[1,2] According to this model, increased hepatic levels of free fatty acid (FFA) consequent to impaired insulin sensitivity in the liver and peripheral tissues may serve as the first hit. The increased hepatocyte FFA load would further increase insulin resistance (IR), steatosis, oxidative stress with lipid peroxidation, endoplasmic reticulum stress, resulting in inflammatory cell accumulation and activation into the liver (second hit). This finally leads to hepatocyte growth arrest or apoptosis, which activates hepatic progenitor cells and associated bile ductular proliferations, cells that initiate inadequate repair by producing a diverse range and high concentrations of profibrogenic cytokines and growth factors that activate hepatic stellate

cells (HSC) and perivascular or portal fibroblasts. The activated HSC themselves can release chemotactic factors that recruit inflammatory cells, creating a deleterious feedback inflammatory loop that leads to fibrogenesis. Collagen and other extracellular matrix components accumulate within the liver, which may result in distortion of the hepatic architecture and finally cirrhosis. Thus, in this "multiple-hit" model IR can be considered as the first step on the pathogenic road leading to NASH, fibrosis and cirrhosis.

However, this "multiple-hit" model has been recently challenged by data suggesting that mechanisms that can drive disease progression can also induce steatosis. Oxidative stress and gut flora/cytokines can induce steatosis as well as necroinflammation and fibrosis. Free fatty acids can initiate hepatocyte apoptosis in addition to being esterified to triglycerides. Endoplasmic stress can also lead to steatosis, oxidative stress, and apoptosis. Since all these mechanisms are important in obesity and IR, it would seem likely that they are the true "first hits" leading to increased hepatic FFA flux and oxidative-, endoplasmic reticulum-, and cytokine-mediated stress that result in both steatosis and progressive liver damage. Steatosis should therefore be considered part of the liver's early "adaptive" response to stress, rather than a first hit in disease progression. Accordingly, while in some situations its severity may act as a biomarker of ongoing injurious and fibrotic mechanisms resulting in disease progression, it should not be considered a sole therapeutic target. Instead attention should be paid on the mechanisms of cellular injury and fibrosis – the "second hits."

Oxidized by-products are harmful adducts that can cause liver injury, resulting in subsequent fibrosis.[3] Lipid peroxidation and oxidative stress up-regulate liver fibrosis via activation of stellate cells and increased production of Transforming Growth Factor-beta.[4] Over expression of uncoupling proteins has been associated with a reduction in generation of reactive oxygen species and Kupffer cell activation, which might attenuate injury in NAFLD. In addition to insulin resistance, several authors have shown that leptin contributes to an insulin-resistant state and might even stimulate fibrogenesis in animal models of NAFLD.[5]

Inflammatory mediators have been implicated in the progression of NAFLD and are the focus for new therapeutics. Pro-inflammatory transcription factors such as Nuclear Factor kappa B (NF-κB) are often elevated in patients with NASH.[6] Adiponectin decreases fatty acid oxidation and inhibits hepatic gluconeogenesis.[7] Both human and mouse models have demonstrated that lower adiponectin levels are associated with increased severity of hepatic inflammation.[8,9] Tumor Necrosis Factor (TNF)α is an inflammatory mediator largely produced by macrophages, but also elaborated by other cells including adipocytes and hepatocytes.[1,10] Elevated levels of TNFα have been detected in obese patients with insulin resistance and NASH.[11,12] TNFα-mediated hepatic injury results from inhibition of mitochondrial electron transport and release of reactive oxygen species that stimulate lipid peroxidation.[10]

Recently, scientists have focused on the role of Kupffer cells in the pathogenesis of NAFLD. Kupffer cells are the resident macrophages of the liver and function in both innate and adaptive immunity as active phagocytosing agents and antigen-presenting cells (via toll-like receptors) to T-cells. Finally, the

proapoptotic gene Bax is upregulated in patients with NASH and alcoholic liver disease.[13] Additionally, caspase levels, by-products of cellular apoptosis, are also increased in these groups of patients.

1.3. ELAFIBRANOR: RATIONALE FOR A MIXED PPAR ALPHA/DELTA AGONIST IN NASH

The GENFIT drug candidate, elafibranor, and its main active circulating metabolite, GFT1007, are dual peroxisome proliferator-activated receptor (PPAR)α/δ modulators with preferential activity on PPARα over PPARδ (about fivefold more potent on human PPAR [hPPAR]α than on hPPARδ). The PPARδ properties of elafibranor and GFT1007 have been demonstrated in both human skeletal muscle cells (a pure PPARδ response) and human hepatocytes (a mixed PPARα/δ response).

The PPARα receptors are most prominently expressed in the liver and can be activated by drugs of the fibrate class. Activation results in increased uptake and oxidation of FFAs, increased triglyceride hydrolysis and upregluation of apolipoprotein (Apo)A-I and ApoA-II. The net effect is fatty acid oxidation, decrease in serum triglycerides, a rise in high-density lipoprotein cholesterol (HDL-C) levels, and an increase in cholesterol efflux. The PPARα activation has also anti-inflammatory effects via inhibition of COX2, IL-6, and C-reactive protein (CRP). Some PPARα compounds have proved their effectiveness in animal models like Methionine-Choline-Deficient diet model or CCl4 in reducing the steatosis. However, clinical trials with fibrates in human NASH have been unimpressive. For example in a pilot study, 12 months treatment with clofibrate in 16 patients with NASH and elevated triglycerides had no impact on liver enzyme elevation or triglycerides levels.[14]

The PPARδ appears to be a powerful metabolic regulator, with actions on fat, skeletal muscle, liver, and heart. Its activation enhances fatty acid transport and oxidation, improves glucose homeostasis via improved insulin sensitivity and inhibition of hepatic glucose output, turns off macrophage inflammatory responses, and dramatically increases circulating HDL-C levels. Thus selective PPARδ agonists have the potential to target multiple components of the metabolic syndrome, including obesity, dyslipidemia, hypertriglyceridemia insulin resistance, and probably NASH.

Accordingly, PPARδ ligands also show promise in chronic inflammatory models of hepatotoxicity.[15] Notably, biomarkers of liver toxicity, including serum alanine aminotransferase (ALT), hepatic TNFα, TNF-like weak inducer of apoptosis receptor, were all higher in carbon tetrachloride-treated PPARδ knockout mice compared to wild-type mice. GW0742 reduced serum ALT, TNFα, S100A6, MCP1, and TNF-like weak inducer of apoptosis receptor in wild-type mice, but not PPARδ knockouts.

Finally, in a short clinical trial, a pure PPARδ agonist, GW501516, has demonstrated efficacy on liver fat content while improving insulin resistance and decreasing γGT.[16]

Considering the emerging role of Kupffer cells in the pathogenesis, 2 recent publications identified PPARδ as a crucial signaling receptor controlling the phenotypic switch between classical pro-inflammatory and alternative anti-inflammatory (M2) macrophages.[17,18] These studies demonstrate that PPARδ encourages

macrophages toward the alternative M2 phenotype, which improves fatty acid metabolism, insulin sensitivity, and suppresses inflammation. The finding raise the possibility that small molecule agonist of PPARδ may be effective therapeutic targets for the treatment of chronic inflammation in the liver.

The match between the activation of PPARα and PPARδ in the liver may thus improve NASH. Accordingly, in several well-established experimental models of NAFLD/NASH and liver fibrosis, treatment with elafibranor confers liver protection both in preventive and therapeutic approaches on established pathologies. These effects have been demonstrated through plasma and hepatic markers, as well as liver macro- and micro- histological examination. These studies have shown that elafibranor acts on several mechanisms involved in NASH pathogenesis: steatosis, inflammation, and fibrosis pathways. Complementary studies have demonstrated that both PPARα-dependent and PPARα-independent mechanisms participate in the beneficial effects of elafibranor on NAFLD/NASH.

1.4. SUMMARY OF NONCLINICAL STUDIES

1.4.1. Pharmacology

Besides hepatoprotection, the efficacy of elafibranor has been assessed in numerous pharmacological preclinical models of metabolic disorders. Briefly, in experimental models of type 2 diabetes, elafibranor has insulin-sensitizing and glucose lowering properties. In db/db mice, a 28-day treatment with elafibranor produced a dose-dependent decrease in fasting plasma glucose and glycated hemoglobin (HbA1c), comparable to the effect of rosiglitazone. However, in contrast to the PPARγ reference agonist, elafibranor did not increase plasma adiponectin, thus ruling out a PPARγ -mediated effect on adipose tissues. Similarly, in ob/ob mice, elafibranor ameliorated plasma glucose and insulin levels without modulating plasma adiponectin or inducing PPAR target genes in adipose tissues.

Besides its effects on NAFLD/NASH and type 2 diabetes, oral treatment with elafibranor in a mouse model of dyslipidemia potently reduced plasma triglycerides and total cholesterol through the induction of PPARα target genes in the liver and by reduction of ApoCIII gene expression. In parallel, elafibranor increased plasma HDL-C levels more potently than the PPARα reference compound fenofibrate. The chronic treatment of these mice fed a high fat diet with elafibranor prevented the development of atherosclerotic plaques in the aorta.

1.4.2. Safety pharmacology

Any potential effect on the cardiovascular, respiratory, and central nervous system has been assessed and no safety issue was identified.

1.4.3. Absorption/distribution/metabolism/excretion studies (ADME)

In animal studies, elafibranor was well and rapidly absorbed although absolute bioavailability was moderate (about 20% to 40%). Elafibranor is extensively metabolized and the activity is mainly carried by

the active metabolite GFT1007. In rat and dog, maximal plasma concentrations and exposure for both elafibranor and GFT1007 linearly increase with the dose after single or repeated administrations. Elafibranor and its metabolites are rapidly cleared from the plasma and they are totally excreted by both fecal and renal route within 48 hours. In the rat elafibranor and/or its metabolites are rapidly excreted into the bile and undergo an extensive entero-hepatic cycle giving support for liver targeting of elafibranor and/or GFT1007. The distribution study in the rat supports the liver targeting of elafibranor and/or its metabolites.

In vitro elafibranor does not inhibit cytochrome p450 (CYP)1A2, CYP3A4, and CYP2D6 with moderate inhibition of CYP2C9 and weak inhibition of CYP2C8, CYP2C19, and CYP4A11. GFT1007 does not produce any inhibition of the CYP450 isoforms 1A2, 3A4, 2C19, and 2D6, and only weak inhibition of CYP2C8 and CYP2C9. Both molecules also show weak inhibition of CYP3A4/5, but only with midazolam as substrate. Thus, the risk of drug-drug interaction due to an inhibition of the main cytochromes involved in drug metabolism should be limited. Potential interaction with CYP2C9 metabolized drugs has been assessed through a clinical study (GFT505-112-8) designed to evaluate potential pharmacokinetic (PK) interaction of elafibranor 120 mg administered for 14 days alone or with a single administration of warfarin. This study demonstrated that elafibranor administration did not affect the PK profile of warfarin (R-warfarin and S-warfarin).

A protein binding study showed that elafibranor and GFT1007 were highly bound to human serum albumin. The risk of drug-drug interaction due to albumin binding should be limited since this binding is not saturable.

In vitro studies have been performed to determine whether elafibranor (GFT505) and it principal metabolite GFT1007 are substrates and/or inhibitors of major drug transporters, in order to assess the potential for drug-drug interaction (DDI). Based on the results of the OATP1B3 transporter inhibition assay, elafibranor (GFT505) has recently been assessed in a follow-up clinical DDI study with the OATP1B3-sensitive substrate, atorvastatin.

For the other drug transporters studied, the interaction observed does not require follow-up studies based on current regulatory guidance.

The metabolic stability and metabolism pathways of elafibranor (GFT505) have been studied on liver microsomes and in primary hepatocytes from rat, dog, mouse, monkey, and human. There was no evidence of the formation of unique human metabolites or metabolites formed at disproportionately higher levels in human hepatocytes than in any other species.

An in vivo study has been performed to compare the bioavailability of ^{14}C-GFT505 in the rat, dog, minipig, and monkey. This study showed that in all species ^{14}C-GFT505 is rapidly absorbed, although absolute bioavailability was moderate (about 20% to 40%).

1.4.4. Toxicology

1.4.4.1. Mutagenicity and genotoxicity

The toxicology program performed according to International Council for Harmonisation (ICH) guidelines demonstrates that elafibranor has no genotoxic or mutagenicity potential.

1.4.4.2. Acute toxicity

According to acute toxicity studies results, it can be concluded that elafibranor is extremely safe when administered as single oral doses in rat and mouse, since no sign of toxicity was detected up to the dose of 1000 mg/kg.

1.4.4.3. Repeated dose toxicity studies

The safety of elafibranor has been assessed in multiple preclinical toxicology studies with repeated-dose oral administration for up to 6 months in rats and 12 months in monkeys. Moreover, two-year repeated-dose carcinogenicity studies in mice and rats have been completed.

The only consistent safety concern raised by these studies is the expected PPARα-associated hepatomegaly, hepatocellular hypertrophy, and liver carcinoma in rodent species (mice and rats). However, it is well known that, compared to nonhuman primates and humans, rodents are highly sensitive to PPARα agonist induced peroxisome proliferation and associated liver side effects. Thus, available information on this class of drug which includes marketed fibrates together with the lack of any liver side effects in monkeys treated with high doses of elafibranor for 1 year support the nonrelevance to human.[19] Overall, these studies did not reveal any other safety issues up to the highest doses tested. Notably, elafibranor did not have any of the known PPARγ-related concerns such as excess in weight gain, hemodilution, edema, cardiomegaly, adiponectin induction, or urinary bladder carcinoma.

1.4.4.4. Phototoxicity studies

The phototoxic potential of elafibranor has been assessed by the in vitro 3T3 NRU phototoxicity test and the UV- Local Lymph Node Assay (LLNA) test in mice. Elafibranor (GFT505), but not its major metabolite GFT1007, showed UVA-dependent cytotoxicity in vitro. The UV-LLNA test was performed in mice with oral dosing for 3 days at up to 800 mg/kg/day elafibranor. Although a very conservative no observed effect level (NOAEL) was set at 400 mg/kg/day based on isolated findings at the highest dose, it is considered that data are more in favor of an absence of phototoxic effect, given the tissue distribution of elafibranor (GFT505), and absence of phototoxicity signal in the clinical studies.

1.5. CLINICAL STUDIES

1.5.1. Phase I program

A Phase I program to assess the safety and tolerability as well as the PK profile of elafibranor has been conducted through 12 clinical trials, one of them ongoing. A total of 621 volunteers were randomized in these studies performed in Phase I centers, including 549 healthy lean subjects, 60 overweight or obese subjects, and 12 patients with type 2 diabetes.

The plasma concentrations of elafibranor and GFT1007 were determined using validated high-performance liquid chromatography tandem mass spectrometry methods. The PK parameters were calculated using a noncompartmental analysis.

In healthy volunteers, the PK of elafibranor and GFT1007 after single administration of elafibranor at rising dose levels were assessed in 2 distinct double-blind, placebo-controlled randomized trials from 10 to 120 mg (GFT505-106-1 and GFT505-108-4). The PK of elafibranor and GFT1007 after repeated doses of elafibranor at rising dose levels were assessed in 3 distinct double-blind, placebo-controlled randomized trials: GFT505-106-2 (5, 10, 20, and 30 mg/d), GFT505-108-4 (40, 60, 80, and 100 mg/d) and GFT505-113-9 (300 and 360 mg/d).

In overweight/obese but otherwise healthy volunteers, the PK of elafibranor and GFT1007 after single administration of elafibranor at rising dose levels from 180 to 300 mg were assessed in a double-blind, placebo-controlled randomized trial (GFT505-111-7). In the same trial, the PK of elafibranor and GFT1007 after repeated doses of elafibranor at dose levels from 120 to 240 mg, were assessed in overweight/obese but otherwise healthy volunteers. Another part of this trial assessed the PK of elafibranor and GFT1007 after repeated doses of elafibranor at 180 mg in type 2 diabetic patients.

The food effect on PK of elafibranor and GFT1007 was assessed in healthy volunteers at the dose of 30 mg elafibranor in a Phase I, randomized, crossover trial (GFT505-106-1).

The PK of elafibranor and GFT1007 obtained after administration of the different formulations used throughout clinical evaluation of elafibranor were compared in dedicated clinical trials in healthy volunteers: GFT505-108-3, GFT505-111-7, and GFT505-115-12. Comparable relative bioavailability was demonstrated.

The lack of PK DDI between elafibranor (80 mg/d) and Simvastatin has been verified (GFT505-109-5).

The lack of effect of a concomitant administration of sitagliptin on elafibranor PK has been verified (GFT505-109-6).

The lack of effect of elafibranor administration (120 mg/d) on the PK and pharmacodynamics (PD) of warfarin has been verified (GFT505-112-8).

The lack of effect of elafibranor administration (180 mg/d) on the PK and PD of atorvastatin has been verified (GFT505-115-11).

The study GFT505-113-9 evaluated the effect of multiple oral doses of elafibranor on the QT/corrected QT (QTc) interval compared to placebo with moxifloxacin (400 mg in single oral dose) as a positive control, in healthy male and female volunteers. No effect of elafibranor on QT/QTc interval at both therapeutic and supratherapeutic doses for 14 days was observed.

The excretion balance of radiocarbon (i.e., the sum of ^{14}C-labeled elafibranor and its ^{14}C-labeled metabolites) and the metabolite profiling and PK of elafibranor after a single oral dose of 120 mg ^{14}C-labeled elafibranor have been assessed (GFT505-114-10). Most of the radiocarbon was excreted in feces (77.1%) and urine (19.3%), giving a recovery of 96.3% of the administered dose. The metabolite profile was assessed in plasma, urine, and feces, and did not highlight any new Phase I metabolite but allowed the identification of new glucuronated metabolites, one of them being the main urinary metabolite (12% of the administered dose).

Part of the study GFT505-115-12 is still ongoing. The objective is to assess the dose linearity after single oral administration of 120, 180, and 240 mg of elafibranor, and the time dependency of the PK parameters after single and multiple oral administration of therapeutic dose of elafibranor.

1.5.2. Phase II program

A Phase II program was initiated to assess the safety, and efficacy profile of elafibranor in patients suffering from cardiometabolic disorders. To date, 5 Phase IIa pilot trials have been completed in which 297 patients were randomized. A Phase IIb trial has recently been completed (Clinical Study Report [CSR] not yet available), and evaluated the efficacy and safety of elafibranor 80 mg and 120 mg on steatohepatitis in 274 patients with NASH.

A Phase IIa pilot study (GFT505-207-1) was first conducted to evaluate the efficacy, safety, and tolerability of elafibranor at 30 mg/d for 28 days in patients with Fredrickson type IIb dyslipidemia. Thirty-seven randomized patients received elafibranor 30 mg (24 patients) or placebo (13 patients) over a 28-day treatment period. Although improvements were observed on primary lipid parameters, these trends were not statistically significant versus placebo.

The Phase IIa study (GFT505-208-3) assessed efficacy and safety in men and postmenopausal women with atherogenic dyslipidemia (high triglycerides, low HDL-C) and abdominal obesity treated once a day for 28 days with 80 mg/d of elafibranor. Ninety-four patients were randomized: 63 patients in the elafibranor 80 mg/d arm and 31 patients in the placebo arm.

The Phase IIa study (GFT505-209-4) assessed efficacy and safety in patients treated for 35 days with elafibranor at 80 mg/d. This study targeted patients with impaired fasting glucose and impaired glucose

tolerance associated with abdominal obesity. Forty-seven patients were randomized: 23 patients in the elafibranor 80 mg/d arm and 24 patients in the placebo arm.

The Phase IIa study GFT505-210-5 assessed efficacy and safety in patients with type 2 diabetes mellitus. Patients were treated once a day for 12 weeks with 80 mg/d of elafibranor. Ninety-seven patients were randomized: 50 patients in the elafibranor 80 mg/d arm and 47 patients in the placebo arm.

The Phase IIa study (GFT505-210-6) was designed to evaluate the safety and efficacy of elafibranor on hepatic and peripheral insulin sensitivity using the gold standard glucose clamp technique in male patients with homeostasis model assessment of insulin resistance (HOMA-IR) >3 and abdominal obesity. Patients were treated once daily (QD) with 80 mg/d of elafibranor or placebo for 8 weeks in a crossover design. In this study, after 8 weeks of treatment, elafibranor significantly improved the response of the liver to insulin action. Indeed, at the first level of insulin perfusion, the insulin-induced decrease in hepatic glucose production was -49±4% after elafibranor versus -34±4% after placebo (p=0.0016). The insulin sensitivity of the muscles and other peripheral tissues measured at the second level of insulin perfusion was also increased by 28% with a significant effect on the glucose infusion rate (3.69±0.31 mg/kg/min after elafibranor versus 3.21±0.31 mg/kg/min after placebo, p=0.048). Moreover, at the end of the treatment period, elafibranor significantly lowered the FFA levels measured at the first insulin level (FFA 0.21 mEq/L after elafibranor versus 0.27 mEq/L after placebo, p=0.006).

The favorable effect of elafibranor on insulin sensitivity and glucose homeostasis was also observed in studies GFT505-209-4 and GFT505-210-5. In prediabetic patients with impaired fasting glucose, impaired glucose tolerance, and abdominal obesity (study GFT505-209-4), treatment with elafibranor 80 mg/d for 28 days led to a significant decrease in fasting plasma glucose (-5%, p=0.04), fasting plasma insulin (-25%, p=0.009), and consequently improvement of the insulin resistance index (HOMA-IR: -31%, p=0.027). In diabetic patients treated for 3 months with 80 mg/d of elafibranor (study GFT505-210-5), oral glucose tolerance test-derived parameters, including area under the time-concentration curve for glycemia, insulinemia and FFA levels, significantly improved.

In all Phase IIa studies, patients treated with elafibranor at 80 mg/d for 1 to 3 months consistently experienced an improvement of the plasma lipid profile, with significant reduction of triglycerides (-20% to -35%), reduction in low-density-lipoprotein cholesterol (LDL-C) (-10% to -15% in prediabetic, insulin-resistant and diabetic patients) and increase in HDL-C (+10% in patients with atherogenic dyslipidemia). In addition, elafibranor treatment consistently increased the anti-atherogenic apolipoproteins (ApoAI and ApoAII) while reducing the pro-atherogenic apolipoproteins (ApoB, ApoCIII, ApoE).

In all Phase IIa studies, elafibranor treatment at 80 mg/d for 1 to 3 months also led to favorable reductions in inflammatory markers. Reduced haptoglobin levels were observed in all Phase IIa clinical trials with elafibranor, with the greatest effect obtained after 3 months of treatment in diabetic patients (-20% in the elafibranor group versus +6% in the placebo group, p<0.001). Similarly, fibrinogen levels were consistently decreased by approximately 10% in all Phase IIa clinical trials with elafibranor, and

high-sensitivity CRP levels were lowered after 3 months of treatment in diabetic patients (-17% in the elafibranor group versus +52% in the placebo group).

Finally, beneficial effects of elafibranor on liver function were consistently observed in all Phase IIa clinical trials of patients treated for 1 to 3 months with 80 mg/d elafibranor. Significant reductions in circulating levels of gamma-glutamyl transferase (GGT) were observed in each study and reached up to -29% in elafibranor treated groups compared to placebo. In addition, in insulin-resistant patients, elafibranor treatment induced a significant reduction in ALT (-20% compared to placebo), while the level of aspartate aminotransferase (AST) was unchanged.

A Phase IIb study in NASH patients (GFT505-212-7) included 274 patients and involved a total of 56 centers in the US and in multiple European countries (France, Belgium, The Netherlands, Italy, UK, Germany, Spain, and Romania). The study evaluated the efficacy and safety of elafibranor at 80 and 120 mg QD for 52 weeks versus placebo in reversing histological steatohepatitis without worsening of fibrosis.

The study analyses showed that elafibranor at 120 mg demonstrates efficacy on the resolution of NASH without worsening of fibrosis in patients with an active disease (NAFLD Activity Score [NAS] score ≥4). Importantly, elafibranor at 120 mg concomitantly improved the cardiometabolic risk profile of NASH patients by decreasing plasma triglycerides, total and LDL-C, increasing HDL-C, and improving inflammation, insulin resistance and glucose homeostasis.

The good safety profile of elafibranor was confirmed in this study. Elafibranor was well tolerated, at both doses. From the start to end of the study, regular safety reviews did not generate any comment or additional request from the Data Safety Monitoring Board (DSMB). The most frequent and expected adverse events were of gastrointestinal nature. Clinical adverse events were generally mild to moderate in severity and were similar in the placebo and treated groups for the most frequently reported treatment-related AEs. Leukocyturia, hypoglycemia, and diabetes mellitus inadequate control were more frequent in elafibranor arms as well as cutaneous rash, arthralgia, decrease in appetite, dizziness and renal impairment which were only reported in the elafibranor treated groups. Serious adverse events (SAE) were reported in 27 patients treated with elafibranor (13 with elafibranor 80 mg/d and 14 with elafibranor 120 mg/d). Of these, only 6 SAEs reported in 4 patients treated with elafibranor were considered as related to treatment. Nineteen patients discontinued the study for safety reason with no imbalance between groups (6 in the placebo arm, 6 in the elafibranor 80 mg arm, and 7 in the elafibranor 120 mg arm).

1.6. CONCLUSION

Clinical data confirmed the beneficial effect of elafibranor in NASH patients, with efficacy on histology associated with improvement on insulin resistance, and with relevant reductions in markers of liver injury such as GGT and ALT, and in inflammatory markers. It demonstrated also improvement in lipid profile

resulting in a beneficial balance between pro and anti-atherogenic markers. Moreover, it highlighted the good safety profile of elafibranor, since no major safety concerns were raised during these studies.

For additional information see Investigator's Brochure.

1.7. RATIONALE FOR STUDY POPULATION

Given the natural fluctuation of the disease for patients with mild NASH (NAS score of 3), phase IIb study results have clearly highlighted that only NASH patients with moderate to severe disease (NAS score≥4) should be treated.

Regarding fibrosis, available data from meta-analyses demonstrate that NASH patients are at greatest risk of progression to advanced fibrosis, cirrhosis, and liver outcomes. Patients with NASH develop progressive fibrosis in 25% to 50% of individuals over 4-6 years, while 15% to 25% of individuals with NASH can progress to cirrhosis.[20] In another study, with a mean follow-up of 13 years, 13.3% of NASH patients with mild to moderate fibrosis (stage 1-2) and 50% of patients with fibrosis stage 3 at inclusion developed cirrhosis.[21]

Considering these data, it is reasonable to include NASH patients with any stage of fibrosis (stage 1 to 3) in the Phase III program, from both safety and prospect for benefit standpoints. However, since in patients with NASH and advanced fibrosis (F2-F3) the probability of developing cirrhosis is much higher than in patients with early fibrosis (F1), the population evaluated for the long-term outcome needs to be based on the advanced fibrosis patients in order to enhance the chances of demonstrating a benefit within a reasonable timeframe.

Accordingly, the target population for the analysis of surrogate endpoint and liver outcomes will be NASH patients with advanced fibrosis (F2-F3). The enrollment of patients with advanced fibrosis for the evaluation of long-term outcomes including progression to cirrhosis should ensure that an expected number of events, calculated based on progression rate for each fibrosis stage, are obtained. Based on the literature,[21,22,23,24,25] in patients with NASH and advanced fibrosis (F2-F3) this progression rate can be estimated at 8% per year for fibrosis stage 3 and 6% per year for fibrosis stage 2, thus an average of 7% for advanced fibrosis.

As a conservative approach, no supplementary percentage was added to the estimated progression rate to histological cirrhosis (7%) for all the other events of the composite endpoint not linked to cirrhosis. Generally, liver decompensation events occur only when cirrhosis is present and the progression rate to the other events is expected to be very low.

A limited number of NASH patients with fibrosis stage 1 and associated comorbidities known to be at risk of fast disease progression will be included in the study as an exploratory group.

Enrollment of female patients will be capped at 40% in each group for this study to mirror the higher prevalence of NASH in males compared to females.[26]

1.8. JUSTIFICATION OF THE SELECTED DOSE

The results obtained in the Phase IIb study evaluating the resolution of NASH clearly demonstrated the superiority of the elafibranor dose of 120 mg over 80 mg on the histological endpoint, regardless of the population selected (Intent-To-Treat [ITT] or Full Analysis Set) or the subgroup tested, indicating that the dose to be used for the Phase III trial should be 120 mg.

To support this assumption, a dose-response modeling was performed based on data obtained in the Phase I clinical program with 14-day repeated dose studies ranging from 5 mg to 360 mg daily dose. In this model, the studied response was the change at endpoint versus baseline in biochemical parameters known to be associated in a dose-dependent manner with elafibranor exposure, such as liver enzymes (ALT, GGT, alkaline phosphatase), plasma lipids (triglycerides, LDL-C, HDL-C) or serum creatinine. Based on this modeling, the optimum dose was consistently assessed as a value of 118 mg. Therefore, given its good safety profile and evidence of efficacy, both supported by the dose-response modeling, 120 mg elafibranor appears to be the most appropriate dose for the upcoming Phase III trial.

1.9. RATIONALE FOR EFFICACY ENDPOINT

1.9.1. Primary endpoint for application under conditional approval

Steatohepatitis is indirectly associated with reduced hepatic survival in NAFLD.[21,27] It drives fibrogenesis, a slow process of hepatic scar formation that can result in cirrhosis and its deadly complications such as liver failure, portal hypertension, and hepatocellular carcinoma. Consequently, clearance of steatohepatitis,[28] i.e., reversal to a normal liver or to steatosis without steatohepatitis – a condition not associated with increased hepatic morbidity or mortality – is expected to improve hepatic prognosis. Natural history studies are now available showing that patients with steatohepatitis but not those with steatosis only (i.e., nonNASH NAFLD) are the ones that progress to cirrhosis and liver-related outcomes. This forms the basis for "resolution of NASH" as a desirable outcome of therapy in the short-term; a concept widely embraced by the academic community and expressed in several scientific society endorsed position papers.[29,30] Based on the recently published recommendations from this workshop,[30] resolution of NASH with no worsening of fibrosis may be an acceptable surrogate endpoint suitable for a Phase III enrolling patients with NASH and fibrosis. Based on recent data that have shown that fibrosis stage of 2 or more is related to liver-related mortality,[22] the "no worsening of fibrosis" should be no progression of one stage in fibrosis.

1.9.2. Primary endpoint for clinical outcome (postapproval confirmation)

The primary endpoint of the Long-term Treatment Period (LTTP) of the study is to evaluate the effect of elafibranor on the progression to cirrhosis, all-cause mortality, and liver-related clinical outcomes as measured by the onset of any of the listed adjudicated events (clinical outcomes composite endpoint).

Primary endpoint events include overall mortality, progression to cirrhosis, and the full list of portal hypertension/cirrhosis related events (liver transplantation, model end stage liver disease (MELD) score ≥15, hepatocellular carcinoma (HCC), and hospitalization due to occurrence of hepatic encephalopathy, variceal bleeding, spontaneous bacterial peritonitis, uncontrolled ascites, hepatorenal syndrome, hepatopulmonary syndrome, and chronic gastrointestinal blood loss due to portal hypertensive gastropathy [provided that these lead to hospitalization or transfusion]).

Singh et al. recently provided a thorough meta-analysis of paired biopsy studies to obtain the most accurate estimate of the fibrosis progression rate in a large cohort of patients with NAFLD.[25] Over 2145.5 person-years of follow-up evaluation, 33.6% had fibrosis progression, 43.1% had stable fibrosis, and 22.3% had an improvement in fibrosis stage. Overall, the annual fibrosis progression rate in a population of patients with NAFLD who had stage 0 fibrosis at baseline was 0.07 stage/year compared to 0.14 stage/year in a population of patients with NASH. In another study of 108 patients, no significant difference in the proportion exhibiting fibrosis progression was found between those with NAFLD or NASH.[31] In the whole cohort, the mean annual rate of fibrosis progression was 0.08 stage/year.

Based on the literature, in patients with NASH and advanced fibrosis (F2-F3), the probability of developing cirrhosis can be estimated at 8% per year for fibrosis F3 and 6% per year for fibrosis F2.[21,22,23,24,25]

In conclusion, the difference in progression to cirrhosis, other liver-related events, and total deaths between treatment and control groups can be considered as a potential clinically meaningful outcome measure for clinical trials. This long-term outcome including progression to cirrhosis is considered acceptable,[30] and required in a postapproval study for treatments approved under conditional approval.

1.10. RATIONALE FOR STUDY DURATION

In accordance with the AASLD and EASL recommendations, 72-weeks of treatment have been defined for the first stage of the study in order to demonstrate the efficacy of elafibranor on resolution of NASH without worsening of fibrosis.

The estimated duration of the LTTP is based on a 7% probability of patients with NASH and moderate and advanced fibrosis (F2-F3) developing cirrhosis or other liver-related events as determined from recently published data [21,22,23,24,25] and the available data of the mortality risk in this patient population.[32,33]

1.11. RATIONALE FOR SAFETY MONITORING

The safety of use of the dose of 120 mg/d of elafibranor during the proposed trial is supported by the chronic toxicity studies and previous Phase I and Phase II trials. Indeed, the toxicology package of elafibranor does not reveal any major safety concern, based on the conclusion that elafibranor-induced liver toxicity in rodents is not relevant to nonprimates (no evidence of liver toxicity in monkeys after 1 year but improvement of liver function markers) and humans (consistent improvement of liver function markers

in all Phase II trials). These toxicology results and conclusions are on-line with the extensive literature on the liver effects of PPAR agonists.

An independent DSMB will be established in order to review the progress of the study and to perform a safety data review (as defined by the DSMB Charter) on a regular basis during the trial to protect patient welfare and preserve study integrity.

Knowing the risks associated with NASH and disease progression, specific attention will be paid to potential hepatotoxicity, liver-related and cardiovascular events.

Given the known effect of elafibranor on serum creatinine increase, special attention will be paid to all the renal safety markers (plasmatic or urinary parameters), including but not limited to albumin-creatinine ratio, cystatin C, neutrophil gelatinase-associated lipocalin (N-Gal), N acetyl β D-glucosaminidase β-NAG, kidney injury molecule-1 (KIM-1). Serum creatinine, modification of diet in renal disease (MDRD) derived estimated glomerular filtration rate (eGFR), and the results of urinalysis (dipstick) will be reported at each visit, as well as blood urea nitrogen. The other markers (plasmatic or urinary) will be assayed in batch and will be reviewed on an ongoing basis through regular safety reviews by the DSMB which includes a nephrologist.

Assays of many other markers are scheduled in order to monitor liver function markers, cardiac safety markers, and to follow up the cardiovascular profile which is known to be at risk in NASH patients.

For cardiac safety, troponin-T and NT-ProBNP will be followed and reviewed on a regular basis by the DSMB. In addition, electrocardiogram (ECG) and blood pressure (BP) will be routinely monitored throughout the study.

Liver function will be monitored throughout the study, by assessment of liver enzymes, bilirubin (total and conjugated), alkaline phosphatase, and international normalized ratio (INR) reported at each visit.

In addition, even if no safety concern has been revealed in the previous clinical program, all the biological parameters that are known to be affected by PPAR agonists will remain monitored in the Phase III trials, such as hematological parameters, adiponectin, or homocysteine.

During the LTTP, patients will be monitored by clinical and biological assessment. A FibroScan® measurement and noninvasive markers assessment will be performed every 24 weeks, and if cirrhosis is suspected, a confirmation by liver biopsy will be performed.

For additional information see Investigator's Brochure.

2. TRIAL OBJECTIVES

2.1. PRIMARY OBJECTIVES

2.1.1. Surrogate endpoint analysis

To evaluate the efficacy of elafibranor 120 mg QD for 72 weeks versus placebo on resolution of NASH without worsening of fibrosis.

- Resolution of NASH is defined as the disappearance of ballooning and disappearance or persistence of minimal lobular inflammation (grade 0 or 1) with an overall pattern of injury not qualifying for steatohepatitis.
- Worsening of fibrosis is evaluated using the NASH Clinical Research Network (CRN) fibrosis staging system and defined as progression of at least 1 stage.

2.1.2. Long-term endpoint

To evaluate the efficacy of elafibranor 120 mg QD versus placebo on clinical outcomes described as a composite endpoint composed of death due to any cause, liver cirrhosis, and the full list of portal hypertension/cirrhosis related events:

- Liver transplantation
- MELD score ≥15
- HCC
- the onset of:
    - variceal bleed
    - hepatic encephalopathy
    - spontaneous bacterial peritonitis
    - ascites
    - hepatorenal syndrome
    - hepatopulmonary syndrome
    - chronic gastrointestinal blood loss due to portal hypertensive gastropathy (provided that these lead to hospitalization or transfusion).

2.2. KEY SECONDARY OBJECTIVE – AT SURROGATE ENDPOINT ANALYSIS

To assess histological changes after 72 weeks of treatment, at the time of surrogate endpoint analysis, on the following endpoint:

- Percentage of patients with improvement of fibrosis of at least 1 stage according to NASH CRN scoring.

2.3. OTHER SECONDARY OBJECTIVES

- To assess histological changes after 72 weeks of treatment and follow-up biopsy on the following endpoints:
    - percentage of patients with resolution of NASH without worsening of fibrosis (follow-up biopsy)
    - percentage of patients with improvement of fibrosis of at least 1 stage according to NASH CRN scoring
    - percentage of patients with at least 1 point improvement in histological scores (NASH CRN scoring: total NAS, steatosis, hepatic ballooning, lobular inflammation), fibrosis (NAFLD Ishak scoring system), or portal inflammation
    - percentage of patients with improvement of NAS of at least 2 points
    - percentage of patients with at least a 1 point improvement in steatosis-activity-fibrosis (SAF) activity score
    - mean changes in NAS, steatosis, hepatic ballooning, lobular inflammation, portal inflammation, SAF activity score
    - changes in area of fibrosis by morphometry
    - mean changes in fibrosis using NASH CRN and NAFLD Ishak scoring.
- To assess the following endpoints at Week 72 and at the end of the LTTP:
    - changes in liver enzymes and liver markers
    - changes in noninvasive markers of fibrosis and steatosis
    - changes in lipid parameters
    - variation in body weight
    - changes in insulin resistance and glucose homeostasis markers
    - changes in inflammatory markers
    - changes in cardiovascular risk profile as assessed by Framingham scores
    - changes in quality of life (36-Item Short-Form Health Survey [SF-36]) questionnaire).
- To assess the onset to:
    - liver cirrhosis
    - death of any cause
    - any portal hypertension or cirrhosis related events
    - cardiovascular events
    - liver-related death events

2.4. EXPLORATORY OBJECTIVES

- To constitute a biobank for discovery and validation of biomarkers in NASH.

2.5. EXPLORATORY OBJECTIVES FOR F1 GROUP

- To explore the following endpoints in F1 patients in the exploratory group at Week 72 and at the end of the LTTP:
    - resolution of NASH without worsening of fibrosis
    - percentage of patients with at least 1 point reduction in NASH CRN fibrosis score and NAFLD Ishak score
    - percentage of patients with at least 1 point improvement in NAS, steatosis, ballooning, lobular inflammation, or portal inflammation
    - percentage of patients with improvement of NAS of at least 2 points
    - percentage of patients with at least a 1 point improvement in SAF activity score
    - mean changes in NAS, fibrosis (using NASH CRN or NAFLD Ishak scoring system), steatosis, hepatic ballooning, lobular inflammation, portal inflammation, and SAF activity score.
    - changes in area of fibrosis by morphometry.
- To explore the following endpoints in F1 patients at Week 72 and after the LTTP:
    - composite endpoint as described in Section 2.1.2.
    - cardiovascular events
    - changes in liver enzymes and liver markers
    - changes in noninvasive markers of fibrosis and steatosis
    - changes in lipid parameters
    - variation in body weight
    - changes in insulin resistance and glucose homeostasis markers
    - changes in inflammatory markers
    - changes in cardiovascular risk profile as assessed by Framingham scores
    - changes in quality of life (SF-36 questionnaire)
- To assess the tolerability and safety.

2.6. SAFETY SECONDARY OBJECTIVES

To assess the tolerability and safety of once a day administration of oral doses of elafibranor 120 mg:

- SAE, AE, physical examination, vital signs, medical history, ECG
- hematological parameters
- liver markers
- renal biomarkers (including urinalysis)
- cardiac biomarkers
- metabolic parameters
- other biochemical safety markers.

3. TRIAL DESIGN

This is a Phase III, randomized, double-blind, parallel groups, placebo-controlled study, evaluating the efficacy and safety of elafibranor 120 mg QD versus placebo in an adult NASH population with fibrosis.

The first double-blind 72-week Treatment Period will assess the efficacy and safety of elafibranor on the resolution of NASH without worsening of fibrosis at the surrogate endpoint efficacy analysis, followed by a LTTP to assess efficacy on progression to cirrhosis, all-cause mortality, and liver-related clinical outcomes as measured by the onset of any of the listed adjudicated events (see Section 2.1.2). The study will terminate upon the 456th patient (excluding exploratory F1 group [see below]) experiencing an event listed in the composite endpoint for long term efficacy evaluation.

It is planned to randomize patients to either active or placebo treatment in a 2:1 ratio, stratified by type 2 diabetes, gender (with a capping of women to 40%), and fibrosis stage. Additional patients with fibrosis stage 1 (10% of sample size calculated for the F2 and F3 patients) and high risk for progression of NASH will also be enrolled for exploratory purposes.

3.1. NUMBER OF PATIENTS

It is planned to randomize 2022 F2/F3 patients to either active (1348 patients) or placebo (674 patients) treatment in a 2:1 ratio. Up to 202 additional patients (a maximum level of 10% of the F2/F3 enrolled patients) with fibrosis stage of 1 and high risk for progression of NASH (NAS ≥5, F1 patients with at least 2 of the following conditions: persistent elevated (absence of normal ALT within the past year, obesity defined by a body mass index (BMI) ≥30, metabolic syndrome [National Cholesterol Education Program's Adult Treatment Panel III {NCEP ATP III definition}], type 2 diabetes, or HOMA-IR >6) will also be enrolled, and followed as an exploratory group. The F1 patients will not be included in the primary surrogate endpoint and final analysis or in the sample size calculation (detailed in Section 9.7). As such a total of 2224 patients will be enrolled, including the exploratory F1 group.

3.2. METHOD OF ASSIGNING PATIENT TO TREATMENT GROUP

Patients who satisfy all eligibility criteria will be randomly allocated to one of the following groups in a 2:1 ratio:

- Elafibranor 120 mg
- Placebo.

Randomization to treatment will be stratified to ensure balance of treatment allocation by the following 3 factors:

- Type 2 diabetes (yes, no)

- Gender (male, female) (with a capping of women to 40%)
- Fibrosis stage (F1, F2, F3) (capped to 202 F1 patients).

Treatment assignments will be made using an interactive voice/web response system (IXRS).

3.3. DOSE ADJUSTMENT CRITERIA

Not applicable. Patients will be randomized to a fixed dose with no allowance for dose adjustment.

3.4. DURATION OF STUDY PARTICIPATION

The estimated duration of the study will be approximately 72 months, based on 456 patients experiencing an event described in Section 2.1.2 at an assumed annual rate event of 7%. However, this may be redefined according to the actual occurrence of events (described in Section 2.1.2) during the confirmatory part of the study (LTTP).

3.5. STUDY PERIODS

The study will comprise 3 periods. The Screening Period (-12 to -1 weeks) will precede a 72-week double-blind First Treatment Period and a LTTP up to the occurrence of a prespecified number of events.

Study procedures are summarized in Table 1, Table 2, and Figure 1.

Schedule:

- Week -12 to Week -1 prior to Randomization: Screening Period (screening visits SV1 to SPV).
- Week 0 to Week 72: First Treatment Period with Elafibranor or placebo for 72 weeks (visits V1 to V7).
- Week 72 to end of study (EOS): LTTP with elafibranor or placebo until 456 patients experience an event listed in Section 2.1.2 (visits V8 to Vn).

3.6. SCREENING PERIOD

3.6.1. Screening visits SV1 (Week -12 to Week -8) and SV2 (Week -12 to Week -4):

The following screening procedures will be performed for all potential patients at SV1 conducted between Week -12 and Week -8 prior to Randomization:

- Signature of informed consent witnessed by the Investigator or designated person. **Note**: The signature of the informed consent may also be performed before SV1.
- Patient number allocation via IXRS.
- Check medical history/demographics.
- Check inclusion/exclusion criteria (described in Section 4).

- Physical examination (described in Section 6.2.1).
- Adequate diet recommendations (described in Section 5.1.1 and APPENDIX II: Adequate diet and lifestyle recommendations), alcohol restrictions (described in Section 5.1.2), and tobacco habits.
- Record vital signs (described in Section 6.2.3).
- Record height, weight, and waist circumference.
- Check concomitant/prior medication (within 6 months prior to Screening) (described in Section 7.12 and APPENDIX III: Permitted/non-permitted medication)
- Check if a liver biopsy with confirmed NASH and fibrosis is available, and, if so send sample for central confirmation of NASH diagnosis (described in Section 6.1.1.2). This historical diagnostic biopsy should be obtained within 6 months prior to the Screening Visit.
- Check AEs from time of Informed Consent Form (ICF) signature (described in Section 6 and Section 8).

The Screening biological assessment (SB1 will be scheduled at SV1).

If no diagnostic liver biopsy (within 6 months of SV1) is available, an additional SV2 visit will be booked at least Week -4 (period between Screening and Week -4) prior to the planned Randomization V1.

The following biological assessments (detailed in Table 2) will be performed at SB1:

- Blood samples (described in Table 2).
- Whole blood, plasma & serum bank samples (only if additional genetic and biomarker ICF signed).
- Urinalysis dipstick.
- Urinary pregnancy test (for women of childbearing potential only [WOCBP]).

Visits SV1 and V1 should be scheduled at least 8 weeks apart in order to have 2 consecutive baseline values of AST, ALT, total bilirubin, and INR for DILI adjudication (using SV1 and V1 kits).

In case of known cured hepatitis C virus (HCV) infection, HCV RNA testing can be done at SV1 without waiting for HCV Ab results.

If needed, a retesting of abnormal HbA1c, or creatine phosphokinase (CPK) results or additional testing of HCV RNA, may be performed during the screening window to determine the eligibility for the study as described in exclusion criteria 5, 12, 30, and 31 (see Section 4.2 and Section 3.11).

At visit SV1, preliminary entrance criteria will be reviewed. Potentially eligible patients will be asked if they agree to participate in the study and sign the ICF. Each patient who has signed the ICF will be allocated a patient number composed of 9 digits which is generated by the IXRS.

- First 3 digits corresponding to the ISO numeric country code (this number will be predefined),
- Next 3 digits corresponding to the site number (this number will be predefined),
- Last 3 digits corresponding to the numerical order of the patient entry at the study site.

A specific IXRS procedure manual will be provided to the Investigator.

3.6.2. Screening Visit SV2 (liver biopsy if required, Week -12 to Week -4):

If no diagnostic liver biopsy within 6 months of SV1 is available, an additional SV2 visit will be booked by at least Week -4 for a liver biopsy to be performed (described in Section 6.1.1.1). Blood samples for coagulation (detailed in Table 2) will be taken and tested at a local laboratory prior to the liver biopsy. Liver biopsy samples will be sent for central confirmation of NASH diagnosis (described in Section 6.1.1.2).

During this visit AEs (from the time of signing the ICF) will also be checked (described in Section 6 and Section 8).

3.6.3. Screening Phone Visit SPV (Week -1):

Upon receipt of the NASH diagnosis confirmation and the SB1 or any retesting/additional testing results from the central laboratory, the Investigator should check the eligibility with inclusion/exclusion criteria.

If patient meets all inclusion criteria and none of the exclusion criteria (clinical, histological, and biological ones), the Investigator will inform the patient of his/her inclusion/noninclusion status by a phone call within 1 week prior to the Randomization Visit V1. In case of ineligibility, the patient should be contacted as soon as possible.

3.7. FIRST TREATMENT PERIOD (WEEK 0 TO WEEK 72)

Efficacy of elafibranor versus placebo on resolution of NASH without worsening of fibrosis will be evaluated in this first period treatment of 72 weeks.

The NASH will be evaluated for inclusion by a centrally-read liver biopsy taken within 6 months prior to Screening (if no historical biopsy is available for NASH diagnosis, a liver biopsy will be performed during the Screening Period) with:

- Presence of NASH, with at least a score of 1 in each component of the NAS (steatosis scored 0 to 3, ballooning degeneration scored 0 to 2, and lobular inflammation scored 0 to 3) AND NAS ≥4.
- Fibrosis stage 2 and 3.

A group of patients (n=202, 10% of each group) with F1 fibrosis, NAS ≥5, and concomitant cardiometabolic comorbidities, which are associated with rapid progression of the disease (listed in Section 3.1), will also be enrolled and followed as an exploratory group.

During these first 72 weeks of treatment, visits will be scheduled every 12 weeks. Clinical and biological evaluation will be performed during this First Treatment Period.

At the end of the 72-week treatment period, a biopsy will be performed for all the patients under treatment in order to evaluate the effect of elafibranor on the liver histology.

When 1023 patients (F2-F3) complete Week 72 (or discontinue early from the study), a surrogate endpoint analysis will be performed and potentially filed for initial market approval under Subpart H or conditional approval, (see Section 9.8.1 for details).

During the First Treatment Period the patients will return to the site for visits every 12 weeks (±1 week) from the Randomization Visit (V1); however the maximum time period between visits is to be 96 days due to the study drug supply provided to the patient.

A diagnosis of any event listed in the primary composite endpoint described in Section 1.9.2 will result in the permanent discontinuation of study drug and discontinuation from the study, following an end of study treatment (EOT) Visit as described in Section 3.9 and Section 5.2.2).

3.7.1. Randomization Visit V1 (Week 0):

Eligible patients will return to the site at the Randomization Visit V1 and then every 12 weeks in the First Treatment Period of the study until the first 72 weeks of treatment (V7) (surrogate endpoint analysis). The patient will be contacted at least 1 week before each visit to be reminded of procedures and investigational product (IP) return.

If the patient is eligible, the Investigator will register the patient for randomization in the IXRS, prior to any other study procedures. If the system confirms the randomization, it will provide the Investigator with a treatment number for the patient.

The following will be performed only at V1:

- Check inclusion/exclusion criteria (detailed in Section 4).
- Randomization to one of 2 treatments groups (elafibranor or placebo in 2:1 ratio, detailed in Section 3.2) via the IXRS.

3.7.2. First Treatment Period visits V1 to V7 (Week 0 to Week 72):

The following procedures will be performed at each of the 12-week visits from V1 to V7:

- IXRS registration
- Physical examination (described in Section 6.2.1)
- Record vital signs and weight (described in Section 6.2.1 and Section 6.2.3)
- Confirmation of adequate diet and lifestyle compliance (described in Section 5.1.1 and APPENDIX II: Adequate diet and lifestyle recommendations), alcohol restrictions (described in Section 5.1.2), and tobacco habits

- Check concomitant/prior medication (described in Section 7.12 and APPENDIX III: Permitted/non-permitted medication)
- Quality of life assessment (V1, V3, V5, and V7, only; described in Section 6.2.6)
- Check AEs (all visits) and occurrence of any clinical outcome (from V2 onwards) (described in Section 6 and Section 8)
- Study placebo or drug dispensation (described in Section 7.6)
- Blood samples (described in Table 2)
- Plasma & serum bank samples (only if additional genetic and biomarker ICF signed)
- Urinalysis and urinary dipstick (described in Table 2)
- Urinary pregnancy test (for WOCBP only)
- Provision of home pregnancy test kits (for WOCBP only)
- Record result of home pregnancy tests (to be performed every 4 weeks [see Figure 2]) since previous visit (for WOCBP only, every visit from V1)
- Record waist circumference (V1, V3, V5, and V7, only)
- 12-lead ECG (V1, V4, and V7, only; described in Section 6.2.4)
- FibroScan (V1 and V7 only, described in Section 6.2.5)
- Drug accountability (every visit from V2).

Additional procedures to be performed at V7 are:

- Liver biopsy (described in Section 6.1.1). **Note:** the liver biopsy may be performed at V7 or during a separate visit that occurs within the V7 window of 72 weeks ± 1 week from V1. Liver biopsy samples will be sent for central histological evaluation.
- Blood samples for coagulation taken (platelets count and prothrombin time [PT (INR)]; described in Table 2) and tested at a local laboratory prior to the liver biopsy.

3.8. LONG-TERM TREATMENT PERIOD

The main objective to be evaluated during the LTTP will be the prevention of progression to cirrhosis, death due to any cause, or to portal hypertension/cirrhosis related events (as described in Section 1.9.2).

After the 72-week biopsy, patients will continue in the double-blind LTTP, receiving the same treatment as assigned at V1 (elafibranor 120 mg or placebo). Patients will be monitored by notably measuring the appearance of cirrhosis (based on FibroScan measurement associated with biological and/or clinical assessments and confirmed by biopsy).

At or after the 72-week biopsy, a diagnosis of any event listed in the primary composite endpoint described in Section 1.9.2 will result in the permanent discontinuation of study drug and discontinuation of the study following the EOT Visit (as described in Section 3.9 and Section 5.2.3).

3.8.1. Long-term Treatment Period visits (V8 to Vn)

Patients will return to the site every 24 weeks during the LTTP. The patient will be contacted at least 1 week before each visit to be reminded of procedures and IP return.

The following procedures will be performed at each visit from V8 to Vn:

- IXRS registration
- Physical examination (described in Section 6.2.1)
- Record vital signs and weight (described in Section 6.2.1 and Section 6.2.3)
- Confirmation of adequate diet and lifestyle compliance (described in Section 5.1.1 and APPENDIX II: Adequate diet and lifestyle recommendations), alcohol restrictions (described in Section 5.1.2), and tobacco habits
- Check concomitant/prior medication (described in Section 7.12 and APPENDIX III: Permitted/non-permitted medication)
- Quality of life assessment (V8, V9, V11, and every 48 weeks thereafter Section 6.2.6)
- Check AEs and occurrence of any clinical outcome (described in Section 6 and Section 8)
- Study placebo or drug dispensation (described in Section 7.6)
- Blood samples (described in Table 2)
- Plasma & serum bank samples (only if additional genetic and biomarker ICF informed consent signed)
- Urinalysis and urinary dipstick (described in Table 2)
- Urinary pregnancy test (for WOCBP only)
- Provision of home pregnancy test kits (for WOCBP only)
- Record result of home pregnancy tests (to be performed every 4 weeks [see Figure 2]) since previous visit (for WOCBP only, every visit from V1)
- Record waist circumference
- 12-lead ECG (every 48 weeks from V9; described in Section 6.2.4)
- FibroScan (described in Section 6.2.5)
- Drug accountability
- Liver biopsy (at approximately 4 years [V13], and in case of suspected liver cirrhosis, described in Section 6.1.1). Liver biopsy samples will be sent for central histological evaluation
- Blood samples for coagulation taken (platelets count and PT [INR]; described in Table 2) and tested at a local laboratory prior to the liver biopsy.

3.8.2. Long-term Treatment Period phone visits (PV1 to PVn)

Phone visits will be scheduled every 24 weeks starting 12 weeks after Visit 7 for data collection on diet and lifestyle, concomitant medications, clinical outcomes, safety, home pregnancy test results, and IP compliance control. If any information during this phone contact requires a visit, the Investigator may decide to perform an unscheduled visit (described in Section 3.11.2). IXRS registration will be performed for each phone visit.

3.9. END OF STUDY TREATMENT VISIT

At the EOS (upon occurrence of the expected number of events), all patients will be asked to stop treatment and undergo an EOT Visit 30 days after the final administration of study drug.

All patients who permanently discontinue their study medication will undergo an EOT Visit 30 days after the final administration of study drug. Patients who permanently discontinue study drug for any reason other than an event listed in the primary composite endpoint for long-term efficacy described in Section 1.9.2 will remain, upon agreement, in the study after the EOT Visit and be followed up to evaluate efficacy outcomes and safety through phone call visits every 24 weeks as described in Section 3.10 and Section 5.2.

If a patient discontinues from the study, every attempt should be made to have the patient return to the site and complete the EOT Visit 30 days after the final administration of study drug. For details of the EOT Visit see Table 1, Table 2, Figure 1, and Figure 2.

The patient will be contacted at least 1 week before the visit to be reminded of procedures and IP return (if required). The following procedures will be performed at the EOT Visit:

- IXRS registration
- Physical examination (described in Section 6.2.1)
- Record vital signs and weight (described in Section 6.2.1 and Section 6.2.3)
- Confirmation of adequate diet and lifestyle compliance (described in Section 5.1.1 and APPENDIX II: Adequate diet and lifestyle recommendations), alcohol restrictions (described in Section 5.1.2), and tobacco habits
- Check concomitant/prior medication (described in Section 7.12 and APPENDIX III: Permitted/non-permitted medication)
- Quality of life assessment (described in Section 6.2.6)
- Check AEs and occurrence of any clinical outcome(described in Section 6 and Section 8)
- Blood samples (described in Table 2)
- Plasma & serum bank samples (only if additional genetic and biomarker ICF informed consent signed)
- Urinalysis and urinary dipstick (described in Table 2),
- Urinary pregnancy test (for WOCBP only)
- Record results of home pregnancy tests (to be performed every 4 weeks [see Figure 2]) since previous visit (for WOCBP only)
- Record waist circumference
- 12-lead ECG (described in Section 6.2.4)
- Drug accountability.

Patients discontinuing study drug or discontinuing the study will be asked to return all used and unused study treatments at the EOT Visit.

3.10. FOLLOW-UP FOR PATIENTS WHO HAVE PERMANENTLY DISCONTINUED STUDY DRUG

Patients who have permanently discontinued study drug due to an event listed in the primary composite endpoint for long-term efficacy described in Section 1.9.2 will be discontinued from the study following the EOT Visit and have no further follow-up.

Patients who have permanently discontinued study drug for any other reason will remain, upon agreement, in the study and will be followed up with phone visits every 24 weeks (±2 weeks from EOT Visit) following the EOT Visit to report safety, diagnosis of cirrhosis and occurrence of clinical outcomes (as listed below) including liver and cardiovascular events until EOS or the occurrence of an event listed in the primary composite endpoint for long-term efficacy (described in Section 1.9.2), whichever is sooner.

The following procedures will be performed during the follow-up phone visit for patients who have permanently discontinued study drug:

- IXRS registration.
- Reporting of safety information regarding:
    - any new AEs
    - resolution of previous AEs
    - change in severity of existing AEs
    - occurrence of any cardiovascular events
    - occurrence of diabetes (for patients not previously diagnosed with diabetes)
    - worsening of diabetes (for patients previously diagnosed with diabetes).
- Reporting of any change in diet and life style factors
- Reporting of any change (quantitative or qualitative) in therapies post study drug discontinuation
- Reporting of cirrhosis diagnosis (patient to be asked if they have had any histological confirmation of cirrhosis)
- Reporting of any of the following events (primary composite endpoint for long-term efficacy evaluation):
    - liver transplantation
    - MELD score ≥15
    - HCC
    - the onset of:
        - variceal bleed
        - hepatic encephalopathy
        - spontaneous bacterial peritonitis
        - ascites
        - hepatorenal syndrome
        - hepatopulmonary syndrome

- chronic gastrointestinal blood loss due to portal hypertensive gastropathy (provided that these lead to hospitalization or transfusion).

- death due to any cause.

3.11. OPTIONAL VISITS

3.11.1. Retesting screening visits

Upon receipt of results from biological assessment done at SV1, and in case a retesting or additional testing is needed according to the selection criteria, an additional visit will be scheduled according to the recommended timeframe for retesting.

Permitted retesting or additional testing in case of abnormal value at SV1 are:

- CPK: can be repeated prior to Randomization (V1) within 1 to 2 weeks after initial test.
- HCV RNA testing: in case positive HVC Ab test at SV1 required latest 2 weeks prior to Randomization (V1).
- HbA1c: can be repeated at the latest 2 weeks prior to Randomization (V1).

Any other retest deemed necessary by the Investigator should be discussed with the Study Medical Monitors.

3.11.2. Unscheduled visits

An unscheduled visit is defined as any visit to the study unit outside of the protocol-evaluation timepoints where the patient is seen by study unit personnel, e.g., when follow-up assessments are required for safety reasons or when repeat measurements are required out of the screening period (either to confirm a measurement or in case of errors, measuring device failure, etc).

Unscheduled visits will be needed for patients who may require further follow-up due to safety.

3.12. EXPLORATORY/ANCILLARY SUBSTUDY

Exploratory substudies might be performed during the study in sites that have the corresponding capability. Specific study documents will be prepared and Institutional Review Board (IRB)/ Independent Ethics Committee (IEC) and authority approvals shall be obtained when applicable.

4. PATIENT SELECTION

A patient will be eligible for the study only if all of the following criteria apply:

4.1. INCLUSION CRITERIA

Patients must meet all of the following inclusion criteria to be eligible for enrollment in the trial:

1. Males or females aged from 18 to 75 years inclusive at first Screening Visit.
2. Must provide signed written informed consent and agree to comply with the study protocol.
3. Females participating in this study must be of nonchildbearing potential or using highly efficient contraception for the full duration of the study and for 1 month after the end of treatment, as described below:
    - Cessation of menses for at least 12 months due to ovarian failure,
    - Surgical sterilization such as bilateral oopherectomy, hysterectomy, or medically documented ovarian failure
    - If requested by local IRB regulations and/or National laws, sexual abstinence may be considered adequate (the reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient)
    - Using a highly effective nonhormonal method of contraception (bilateral tubal occlusion, vasectomized partner, or intra-uterine device)
    - Double contraception with barrier AND highly effective hormonal method of contraception (oral, intravaginal, or transdermal combined estrogen and progestogen hormonal contraception associated with inhibition of ovulation; oral, injectable, or implantable progestogen-only hormonal contraception associated with inhibition of ovulation; or intrauterine hormone-releasing system). The hormonal contraception must be started at least 1 month prior to Randomization.
4. Histological confirmation of steatohepatitis on a diagnostic liver biopsy by central reading of the slides (biopsy obtained within 6 months prior to Screening or during the Screening Period) with at least 1 in each component of the NAS (steatosis scored 0-3, ballooning degeneration scored 0-2, and lobular inflammation scored 0-3).
5. NAS ≥4.
6. Fibrosis stage of 1 or greater and below 4, according to the NASH CRN fibrosis staging system.
   For patients with fibrosis stage 1, only patients at high risk of progression will be included meaning with a NAS ≥5 and at least 2 of the following conditions: persistent elevated ALT (absence of normal ALT within the past year), obesity defined by a BMI ≥30, metabolic syndrome (NCEP ATP III definition), type 2 diabetes, or HOMA-IR >6.
7. Patients in whom it is safe and practical to proceed with a liver biopsy, and who agree to have:

- 1 liver biopsy during the Screening Period for diagnostic purpose (if no historical biopsy within 6 months before screening is available)
- 1 liver biopsy after 72-weeks of treatment for assessment of the treatment effects on NASH
- a final liver biopsy after approximately 4 years of treatment (V13), unless a liver biopsy has already been performed within the past year
- 1 liver biopsy performed only in the case of suspicion of cirrhosis (to have a histological confirmation.

8. If a patient is treated with 1 of the following drugs: vitamin E (>400 IU/day), polyunsaturated fatty acids (>2 g/day), or ursodeoxycholic acid; a stable dose from at least 6 months prior to diagnostic liver biopsy is required.
9. For patients with type 2 diabetes, glycemia must be controlled. If glycemia is controlled by antidiabetic drugs, change in anti-diabetic therapy must follow these requirements:
    - no qualitative change 6 months prior to diagnostic liver biopsy up to Randomization (i.e., implementation of a new anti-diabetic therapy) for patients treated with metformin, gliptins, sulfonylureas, sodium/glucose cotransporter (SGLT) 2 inhibitors, glucagon-like peptide (GLP)-1 agonists, or insulin. Dose changes of these medications are allowed in the 6 months prior to diagnostic liver biopsy, except for GLP-1 agonists, which must remain on stable dose in the 6 months prior to diagnostic liver biopsy.
    - no implementation of GLP-1 agonists and SGLT2 inhibitors up to 72 weeks of treatment (V7).

    Initiation of any other antidiabetic drugs is allowed after Randomization based on treating physicians' judgment, except for glitazones which are prohibited 6 months prior to diagnostic liver biopsy until the end of treatment.

4.2. EXCLUSION CRITERIA

Patients who meet any of the following criteria will be excluded from entering the study:

1. Known chronic heart failure (Grade I to IV of New York Heart Association classification).
2. History of efficient bariatric surgery within 5 years prior to Screening, or planned bariatric surgery in the course of the study.
3. Uncontrolled hypertension during the Screening Period despite optimal antihypertensive therapy.
4. Type 1 diabetes patients.
5. Patients with HbA1c >9.0%. If abnormal at the first Screening Visit, the HbA1c measurement can be repeated at the latest 2 weeks prior to Randomization. A repeated abnormal HbA1c (HbA1c >9.0%) leads to exclusion.
6. Patients receiving thiazoledinediones (glitazones [pioglitazone, rosiglitazone]), unless the drug was discontinued at least 6 months before the diagnostic liver biopsy.

7. Patients with a history of clinically significant acute cardiac event within 6 months prior to Screening such as: stroke, transient ischemic attack, or coronary heart disease (angina pectoris, myocardial infarction, revascularization procedures).
8. Weight loss of more than 5% within 6 months prior to Randomization.
9. Compensated and decompensated cirrhosis (clinical and/or histological evidence of cirrhosis). Notably, NASH patients with fibrosis stage = 4 according to the NASH CRN fibrosis staging system are excluded.
10. Current or recent history (<5 years) of significant alcohol consumption. For men, significant consumption is typically defined as higher than 30 g pure alcohol per day. For women, it is typically defined as higher than 20 g pure alcohol per day. See APPENDIX IV: Alcohol comparison table.
11. Pregnant or lactating females or females planning to become pregnant during the study period.
12. Other well documented causes of chronic liver disease according to standard diagnostic procedures including, but not restricted to:
    - Positive hepatitis B surface antigen (HBsAg)
    - Positive HCV RNA, (tested for in case of known cured HCV infection, or positive HCV Ab at Screening)
    - Suspicion of drug-induced liver disease
    - Alcoholic liver disease
    - Autoimmune hepatitis
    - Wilson's disease
    - Primary biliary cirrhosis, primary sclerosing cholangitis
    - Genetic homozygous hemochromatosis
    - Known or suspected HCC
    - History or planned liver transplant, or current MELD score >12.
13. Where applicable, patients not covered by Health Insurance System and/or not in compliance with the recommendations of National Law in force applicable to clinical trials.
14. Patients who cannot be contacted in case of emergency.
15. Known hypersensitivity to the investigation product or any of its formulation excipients.
16. Patients with previous exposure to elafibranor.
17. Patients who are currently participating in, plan to participate in, or have participated in an investigational drug trial or medical device trial containing active substance within 30 days or five half-lives, whichever is longer, prior to Screening.

Concomitant medications (see APPENDIX III: Permitted/non-permitted medication):

18. Fibrates are not permitted from 2 months before Randomization. Patients that used statins, ezetimibe, or nonfibrate lipid lowering drugs before Screening may participate if the dosage has been kept constant for at least 2 months prior to Screening.

19. Currently taking drugs that can induce steatosis/steatohepatitis including, but not restricted to: corticosteroids (parenteral & oral chronic administration only), amiodarone (Cordarone), tamoxifen (Nolvadex), and methotrexate (Rheumatrex, Trexall), which are not permitted 30 days prior to Screening and up to end of treatment.
20. Currently taking any medication that could interfere with study medication absorption, distribution, metabolism, or excretion or could lead to induction or inhibition of microsomal enzymes, e.g., indomethacin, which are not permitted from Randomization until end of treatment.

Associated illnesses or conditions:

21. Any medical conditions that may diminish life expectancy to less than 2 years including known cancers.
22. Evidence of any other unstable or, untreated clinically significant immunological, endocrine, hematological, gastrointestinal, neurological, neoplastic, or psychiatric disease
23. Mental instability or incompetence, such that the validity of informed consent or ability to be compliant with the study is uncertain.

In addition to the above criteria, patient should not present any of the following biological exclusion criteria:

24. Positive anti-human immunodeficiency virus (HIV) antibody.
25. AST and/or ALT >10 x upper limit of normal (ULN).
26. Conjugated bilirubin >1.50 mg/dL due to altered hepatic function. Note: Gilbert Disease patients are allowed into the study.
27. INR >1.40 due to altered hepatic function.
28. Platelet count <100,000/mm3 due to portal hypertension.
29. Serum creatinine levels >1.53 mg/dL in males and >1.24 mg/dL in females.
30. Significant renal disease, including nephritic syndrome, chronic kidney disease (defined as patients with markers of kidney damage or eGFR of less than 60 ml/min/1.73 m2).
31. Unexplained serum CPK >3 x the ULN. In case of explained elevated CPK >3 x the ULN, the measurement can be repeated prior to Randomization. In this case, retest should be performed within 1 to 2 weeks after initial test. A CPK retest >3 x ULN leads to exclusion.

5. TRIAL PROCEDURES

The procedures performed at each visit are summarized in the study schedules (see Table 1, Table 2, Figure 1, and Figure 2) and in Section 3.

The Investigator will be asked, whenever possible, to schedule patient visits at the same time of day for each patient. A patient may be seen at any time for reasons of safety.

During each visit, lifestyle and study recommendations will be repeated, vital signs will be measured, and the patient will be queried in the form of an open question regarding new or continuing events.

Procedures for premature discontinuation after SV1 are described in Section 5.2.

5.1. LIFESTYLE RECOMMENDATIONS AND STUDY RECOMMENDATIONS

5.1.1. Standard diet and exercise recommendations

Standard diet and exercise recommendations given by the Investigator during SV1 will be given at the beginning of each patient's participation and will be maintained throughout the study. These recommendations will be based on Therapeutic Lifestyle Change (TLC) counseling (or local equivalent) according to NCEP ATP III guidelines. The essential components of TLC and the macronutrient recommendations for the TLC diet are detailed in APPENDIX II: Adequate diet and lifestyle recommendations.

Assessment of dietary and lifestyle compliance will occur at each visit by asking the patient 2 questions to confirm if they have remained compliant to the diet and lifestyle recommendations. A yes/no response will be recorded in the electronic care report form (eCRF).

5.1.2. Dietary, fluid, and lifestyle restrictions

The following restrictions should be applied to patients in this trial from SV1 through to the end of the study:

- Patients will be required to fast (no food or drink other than water) for at least 12 hours prior to all blood sampling. As such, patients should not consume any breakfast or take any medication (including study medication) in the morning prior the blood sampling. In case the patients do not fast before a visit, a new appointment will be scheduled within 7 days.
- On each study visit day, study treatment will be taken under fasting conditions after the blood sampling (which corresponds to the day of the visit).
- During the 48 hours preceding each study visit, patients should not perform strenuous exercise.
- Patients are to avoid consumption of dietary supplements such as anti-oxidant (including, but not limited to Vitamin A, Vitamin C, provitamin A, selenium, and polyphenol).

- Alcohol consumption should be limited during the study duration and registered in the eCRF. Alcohol consumption of more than 20 g per day for women and 30 g per day for men is considered abusive (see APPENDIX IV: Alcohol comparison table). A standard drink is equal to 14.0 grams (0.6 ounces) of pure alcohol. Generally, this amount of pure alcohol is found in:
    - 12-ounces/350 ml of beer (5% alcohol content)
    - 5-ounces/150 ml of wine (12% alcohol content)
    - 1.5-ounces/50 ml (40% alcohol content) distilled spirits or liquor (e.g., gin, rum, vodka, whiskey).

Concomitant therapy is restricted and any change to treatment or introduction of a new treatment should be discussed with the Investigator before doing so (see Section 7.12 and APPENDIX III: Permitted/non-permitted medication).

5.1.3. Home pregnancy test for women of childbearing potential

Women of childbearing potential are required to perform a pregnancy test every 4 weeks. Home pregnancy test kits will be supplied at each visit to WOCBP and these are to be performed as per the kit instructions every 4 weeks between study visits. Negative results are to be reported at the next scheduled visit or telephone visit (see Table 1 and Figure 2). In the event of a positive result the patient must discontinue study drug immediately and report the result to the Investigator as soon as possible (see Section 8.6.1)

5.1.4. Sun exposure

As a conservative approach patients will be advised to avoid extended ultra-violet light exposure without protection from V1 through to the end of the study (see Section 1.4.4.4).

5.2. PATIENT WITHDRAWAL AND PATIENT TREATMENT DISCONTINUATION RULES

5.2.1. Handling of patient withdrawal

Patients will be informed that they have the right to discontinue the study at any time, for any reason, without affecting future management and treatment.

5.2.2. Permanent discontinuations of study drug

In some instances, it may be necessary for a patient to permanently discontinue study drug. The patient may be discontinued from study drug at any time at the discretion of the Investigator or Sponsor for safety, behavioral, or administrative reasons. In keeping with the ITT analysis, the patient will not be permanently discontinued from the study.

The reason for permanent discontinuation of study drug should be documented in the eCRF and the Medical Monitor informed. If the discontinuation of study drug is due to an AE, the event should be documented in the eCRF.

Some possible reasons that may lead to permanent early study drug discontinuation include:

- Occurrence of any event listed in the composite endpoints for long-term efficacy evaluation (see Section 1.9.2)
- In the opinion of the Investigator, any AE, SAE (described in Section 8), or significant change in a laboratory value that warrants permanent discontinuation of study drug therapy. Investigators are advised to call the Medical Monitor prior to making such a decision
- Occurrence of repeated hypoglycemic episodes without possibility for a down titration of background therapy that may put the patient at risk with continued participation
- Non-permitted concomitant medication (described in Section 7.12 and APPENDIX III: Permitted/non-permitted medication)
- Female patients who are pregnant (see Section 8.6.1) or are breastfeeding or who do not agree to use a reliable method of birth control during the study will be permanently discontinued from study drug
- Non-compliance with the study treatment
- Uncooperative patient
- The patient requests to stop study drug permanently.

Patients permanently discontinued from study drug will be requested to stop taking study drug and attend an EOT Visit 30 days after the last administration of study drug (described in Section 3.9).

If the study drug is discontinued due to the occurrence of any event listed in the composite endpoints for long-term efficacy evaluation (see Section 1.9.2), the patient will also be discontinued from the study with no further follow-up after the EOT Visit.

If the study drug is discontinued due to any reason other than the occurrence of any event listed in the composite endpoints for long-term efficacy evaluation, the patient will undergo, if agreed, telephone visits every 24 weeks (described in Section 3.10) after the EOT Visit until the EOS or the occurrence of any event listed in the primary composite endpoints for long-term efficacy evaluation (see Section 1.9.2), whichever is sooner.

5.2.3. Patient discontinuation from the Study

Patient discontinuation prior to the patient's completion of the study is expected to be low, occurring if the patient withdraws consent, or if enrollment in any other clinical trial involving an investigational product, or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study, occurs.

At the time of discontinuing from the study, the Medical Monitor and IXRS should be contacted, and, if possible, an EOT Visit should be conducted (see Section 3.9). The patient will be permanently discontinued from the study at that time with no further follow-up and the date the patient is withdrawn from the study

and the reason for withdrawal should be appropriately documented in the eCRF. During the study close-out period, survival status will be collected within legal and ethical boundaries for all patients randomized who withdrew participation from the study.

Where possible, patients withdrawn from the study will be followed until resolution of all their SAEs or until the unresolved SAEs are judged by the Investigator to have stabilized.

5.2.4. Patients lost to follow-Up

A patient would be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. Site personnel are expected to make diligent attempts to contact patients who fail to return for a scheduled visit or were otherwise unable to be followed up by the site. Vital status will be collected within legal and ethical boundaries for all patients randomized, including those who did not get study drug. Vital status will be searched in public sources during the study close-out period. If vital status is determined, the patient will not be considered lost to follow-up.

5.2.5. Replacement

No patient replacements are permitted in this study.

5.2.6. Premature discontinuation of the study

Premature termination of this clinical trial may occur because of a Regulatory Authority decision, change in opinion of the IRB/IEC, drug safety problems, DSMB recommendations, or at the discretion of the Sponsor. In addition, the Sponsor retains the right to discontinue development of the study treatment at any time.

The Sponsor reserves the right to discontinue the trial prior to inclusion of the intended number of patients, but intends only to exercise this right for valid scientific or administrative reasons. After such a decision, the Investigator must contact all participating patients within a reasonable period of time. As directed by the Sponsor, all trial materials must be collected and all eCRFs completed to the greatest extent possible.

Furthermore, the Investigator can decide to prematurely discontinue the study. In that event, the Investigator must notify the Sponsor immediately of his/her decision and give the reason in writing. Prompt compliance with this requirement is essential so that the Sponsor may comply with its regulatory obligations.

In all cases, ethics committee (IRB/IEC) and Health Authorities should be informed.

If the Investigator decides to prematurely discontinue the study, all test articles, eCRFs, and related study materials must be returned to the Sponsor.

5.3. PATIENT RESCREENING

Re-screening is allowed in a screen failed patient if there is a change in the situation of the patient which allows him/her to fulfill inclusion/exclusion criteria. This will need sponsor approval. In case of re-screening the patient will need to sign a new informed consent and will be entered as a new patient, with a new patient number.

6. ASSESSMENTS

6.1. EFFICACY AND SAFETY ASSESSMENTS

6.1.1. Histological assessments

A liver biopsy (see Section 6.1.1.1 for recommendations) will be performed:

- At baseline
- After 72 weeks of treatment
- After approximately 4 years of treatment (V13) unless a biopsy has been performed within the previous year.
- In the case cirrhosis is suspected at any interim visit during the LTPP (based on FibroScan and/or clinical and biological assessments)

A Laboratory Manual will be provided to each trial site. The manual will outline the collection process, and shipping requirements for the specific central laboratory.

6.1.1.1. Recommendations related to liver biopsy

Before performing a percutaneous liver biopsy, there must be a clearly defined indication for the biopsy, and the risks to the patient should not outweigh the potential benefits. This will be assessed by the investigator according to local practice.

The patient's platelet count and PT should be checked according to local hospital standards before the date of liver biopsy. Local guidelines and thresholds for hemostatic parameters should be used as they are in everyday clinical practice. Usually a platelet count >80,000/mm^3, a PT >60% or longer by no more than 4 seconds over the control, and a normal bleeding time are acceptable for performing percutaneous liver biopsy in a patient that has stopped taking any antiaggregant therapy for >5 days. If these conditions are not all respected, a safer option would be to perform the liver biopsy by transjugular route, when available.

Sedation is recommended to be given for percutaneous liver biopsy, and should be given with caution in liver disease.

The recommended biopsy procedure to be applied is:

- Needle core biopsy
- Biopsy obtained with a 16 or lower gauge needle
- A tissue core ≥2 cm long (≥10 portal tracts) represents optimal biopsy length
- Preferably obtain biopsy from the right lobe. If left lobe biopsy is used for inclusion, a left lobe biopsy should be used for future biopsies.

Post-biopsy observation: It is recommended that the patient should remain in hospital at least for 6 hours after the procedure.

The biopsies will be sent to the central laboratory and then to a central reader who will read the biopsies to determine the eligibility to the study according the fibrosis stage and consistency with NASH diagnosis. Biopsy slides will be blinded for patient and visit identification prior to central reading.

In case the liver biopsy fragment is too small or of bad quality, thereby precluding adequate reading, other available slides or new slides to be prepared from an available block of tissue may be requested to the site.

6.1.1.2. Liver biopsy reading for NAS and NASH CRN fibrosis score

Histological changes from baseline to Week 72 and any follow-up biopsy will be evaluated. Liver biopsy samples will be sent to the central pathology laboratory (Hôpital Beaujon, 100 Boulevard du Général Leclerc, 92110 Clichy – France) where they will be read and scored. Scores for total NAS, steatosis, ballooning, lobular inflammation, or portal inflammation, as well as fibrosis scores (both by NASH CRN scoring system, and NAFLD Ishak scoring system) and fibrosis area by morphometry will be evaluated.

6.1.2. Biological assessments

All blood samples for efficacy and/or for safety assessment (as described in Table 2) will be returned and centralized by the central laboratory (BARC: Ghent – Belgium, New York – USA, Sydney – Australia, or Johannesburg – South Africa) and specific analyses will be performed by another laboratory (GENFIT-Loos, France).

A laboratory manual will be provided to each trial site.

The manual will outline the collection process and shipping requirements for the specific central laboratory. Blood sampling will be performed by trained personnel at each site. Blood samples will be processed and shipped as outlined in the laboratory manual. Refer to the laboratory manual for exact amounts of blood required for each test.

For all visits, reportable laboratory results (except serology) will be available at sites approximately 24 hours after receipt of samples. Final results will be sent to sites. Laboratory reports should be reviewed, signed, and dated by the Investigator as soon as they are received. The Investigator should comment upon out of range parameters and assess clinical significance.

The option to retest during the study is left to the Investigator's judgment. During Screening, retesting (to be performed at retesting screening visits) is limited to HbA1c, CPK, and HCV RNA, as described Section 3.11. Any other retest deemed necessary by the Investigator should be discussed with the Study Medical Monitors.

In case the lab sampling may not be performed at the scheduled visit, patients should come back to the site within 7 days of the visit for lab sampling.

6.1.2.1. Laboratory assessments

Clinical laboratory evaluations (including hematology, blood chemistry, and urinalysis) will be measured at every visit as described in Table 2.

Hematology and urinalysis (dipstick) will be measured at all visits. Both blood and urine sample will be transported to the central laboratory for testing and analysis. At Screening, the Screening Visit 1 chemistry panel will be measured.

The V1 to Vn total chemistry panel and urine analysis will be measured at all visits from V1 to EOT visits. It is recommended to collect first morning urine samples for urinalysis.

6.1.2.2. Urinary pregnancy tests

Urinary pregnancy tests will be supplied to each site to perform a pregnancy diagnostic at each visit during the study on WOCBP. These tests will also be given to the WOCBP to perform a pregnancy test at home every 4 weeks in between visits (see Section 5.1.3).

6.1.2.3. Serology (SB1)

Screens for a hepatitis panel and HIV antibodies will be performed at SV1:

- HIV ab I/II
- HBsAg
- HCV ab (in case of known cured HCV infection, HCV RNA can be tested directly at SV1; otherwise, HCV RNA should be tested at a Retesting Screening Visit, only in case HCV ab>0 at SV1 [see Section 3.11.1])

6.1.2.4. Other parameters

Liver markers, calculated fibrosis and steatosis index, safety, and inflammatory markers, as well as special glycemic and lipid parameters, will be measured at V1, V3, V5, and V7 during the First Treatment Period, at each visit during LTTP, and at the EOT visit. CHI3L1 will only be tested at V1, V7, and V13 (at the time of the approximate 4 year biopsy).

6.1.3. Constitution of biobank

In order to be able to test other specific parameters which could be of interest regarding the elafibranor development program or regarding diagnosis, prevention, or treatment of NASH or other related diseases, an additional amount of serum & plasma will be kept at each visit (including screening visits) from patients who have given their consent for these additional analyses by signature of the genetic and biomarker ICF.

These samples will be used:

- To discover or validate biomarkers in NASH and related diseases.
- To investigate the role of selected single nucleotide polymorphisms in the response to treatment.

These samples will be destroyed 3 years after study results at the latest.

6.2. OTHER SAFETY ASSESSMENTS AND ONGOING SAFETY MONITORING

6.2.1. Physical examination

A physical examination will be performed and weight measured at each visit (with the exception of the potential SV2). Height will be measured at SV1 only.

The patient's weight will be measured under the same conditions at each visit. Where possible, the scale for weight must be the same for a given patient throughout the visits.

6.2.2. Waist circumference

Waist circumference will be measured at the midpoint between the lateral iliac crest and the lowest rib in cm during expiration. The measuring tape should be snug but not compressing the skin and held parallel to the floor. The measurement is to be made at normal respiration.

6.2.3. Vital signs

Blood pressure (mmHg) and pulse rate (beats per minute) will be measured at each visit (with the exception of the potential SV2 visit) according to the "Recommendations for Blood Pressure Measurement in Humans and Experimental Animals" published in an American Heart Association scientific statement.

6.2.3.1. Important points for clinical blood pressure measurement

- The patient should be seated comfortably with the back supported and the upper arm bare without constrictive clothing. The legs should not be crossed.
- The arm should be supported at heart level, and the bladder of the cuff should encircle at least 80% of the arm circumference.
- When using a mercury sphygmomanometer, the mercury should be deflated at 2 to 3 mm/s, and the first and last audible sounds should be taken as systolic and diastolic pressure. The column should be read to the nearest 2 mmHg.
- Neither the patient nor the observer should talk during the measurement.

Systolic BP and diastolic BP will be measured after 5 minutes rest in the seating position with a standard mercury sphygmomanometer or a validated sphygmomanometer. Where possible, the validated manometer should be the same for a given patient throughout the visits.

6.2.4. Electrocardiogram

A standard 12-lead ECG will be obtained at V1, V4, and V7 in the First Treatment Period, every 48 weeks in the LTTP starting at V9, and at the EOT visit.

Electrocardiograms will be recorded using 12-lead ECG recorders following 10 minutes rest in the supine position. A minimum of 3 cycles will be recorded per lead.

The ECGs will be analyzed by the Investigator. Any potential clinical significance of ECG changes will be determined by the Investigator with relation to the patient's medical history, physical examination, and concomitant medications and recorded in the eCRF.

6.2.5. FibroScan

A FibroScan exam will be performed at V1 and V7 in the First Treatment Period and at each visit in the LTTP under 2 hour fasting conditions. Where possible, FibroScan must be done at the day of visit. Otherwise, it can be performed within 7 days around the visit date.

In case of result ≥14 kPa or of sudden increase from previous measurement, a repeated measurement will be required 4 weeks later (to be performed at an unscheduled visit).

If at baseline, the measurement gives a value ≥14 kPa but without being associated with confirmed histological cirrhosis, a FibroScan measurement will be continued as planned in the protocol but will not be used for the detection of cirrhosis (no repeat test required for patients with baseline≥14 kPa at V1).

6.2.6. Quality of life questionnaire

A standardized and validated questionnaire for quality of life (SF-36) will be completed by patients at V1, V3, V5, and V7 in the First Treatment Period, and V8, V9, V11, and every 48 weeks thereafter in the LTTP until, and including the EOT visit.

6.3. IMPORTANT SPECIFIC BIOLOGICAL CONSIDERATIONS AND PATIENT DISCONTINUATION RULES

6.3.1. Creatine phosphokinase

If at any visit during the treatment periods, a patient experiences diffuse myalgia, muscle tenderness, and/or marked increase in muscle CPK values (≥3 x ULN and ≤5 x ULN), an additional visit and test within 3 to 7 days must be performed. If, during that visit, the patient still experiences diffuse myalgia, muscle tenderness and/or marked increase in muscle CPK values (≥3 x ULN and ≤5 x ULN), myopathy must be considered and the patient must be discontinued from study treatment immediately and followed up as described in Section 5.2.2.

If at any visit during the treatment periods, a patient experiences marked increase in muscle CPK values >5 x ULN, unexplained by strenuous exercise or trauma, the patient must be discontinued from study treatment immediately and followed up as described in Section 5.2.2. In case of exercise and/or trauma, the CPK should be repeated once weekly to verify decrease of CPK, until CPK lowers to ≤5 x ULN.

6.3.2. Liver function monitoring

All liver decompensation events included in the composite efficacy endpoint (Section 1.9.2) will be adjudicated by the Clinical Events Committee (CEC; see Section 6.5), as well as all DILI events (see Section 6.5).

For DILI adjudication, assessment may be performed using as baseline value the average obtained from measurements at the SV1 and V1 visits (described in the CEC Charter).

In all cases, whether baseline AT values are normal or elevated, an increase of AT >10 x ULN will lead to permanent discontinuation of the patient from study drug, and scheduling of EOT visit (Section 3.9).

6.3.2.1. Monitoring of patients with normal baseline aminotransferase values

Liver function monitoring requirements for patients with normal baseline AT values at V1 who at any visit from V2 onwards during the treatment periods exhibit:

- Increase in AT to ≤3 x ULN: no additional action required, schedule next visit as per assessment schedule
- Increase in AT to >3 x ULN but ≤5 x ULN: retest after 48 to 72 hours
  If during the following retest:
  - AT remains >3 x ULN but ≤5 x ULN: continue the drug with close serial monitoring (once a week)
  - AT increases to >5 x ULN: permanently discontinue patient from study drug and schedule EOT Visit (see Section 3.9 and Section 5.2.2).
- Increase in AT >5 x ULN: retest after 48 to 72 hours
  If during the following retest:
  - AT remains >5 x ULN: permanently discontinue patient from study drug and schedule EOT Visit (see Section 3.9 and Section 5.2.2)
  - AT reduces to ≤5 x ULN: continue the drug with close serial monitoring (once a week).
- Increase in AT >3 x ULN AND increase in total bilirubin > 2 ULN: permanently discontinue patient from study drug and schedule EOT Visit (see Section 3.9 and Section 5.2.2).
- Increase in AT >3 x ULN AND increase in INR>1.5: permanently discontinue patient from study drug and schedule EOT Visit (see Section 3.9 and Section 5.2.2).

- Increase in AT >3 x ULN AND fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%): permanently discontinue patient from study drug and schedule EOT Visit (see Section 3.9 and Section 5.2.2).

6.3.2.2. Monitoring of patients with increased baseline aminotransferase values

Liver function monitoring requirements for patients with increased AT baseline values at V1 who at any visit post V1 onwards during the treatment periods exhibit:

- Increase in AT to ≤3 x baseline value: no additional action required, schedule next visit as per assessment schedule
- Increase in AT to >3 x baseline value but ≤10 x ULN: retest after 48 to 72 hours
    - AT remains >3 x baseline value but ≤ 10 x ULN: continue the drug with close serial monitoring (once a week)
    - AT increases > 5 x baseline value or >10 x ULN: permanently discontinue patient from study drug and schedule EOT Visit (see Section 3.9 and Section 5.2.2).
- Increase in AT >3 x baseline value AND increase in total bilirubin > 2 x ULN: permanently discontinue patient from study drug and schedule EOT Visit (see Section 3.9 and Section 5.2.2).
- Increase in AT >3 x baseline value AND increase in INR>1.5: permanently discontinue patient from study drug and schedule EOT Visit (see Section 3.9 and Section 5.2.2).
- Increase in AT >3x baseline value AND fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%): permanently discontinue patient from study drug and schedule EOT Visit (see Section 3.9 and Section 5.2.2).

6.3.3. Threshold for diagnosis of cirrhosis

A FibroScan and serum markers assessments will be performed every 24 weeks at each visit in the LTTP.

In case of FibroScan ≥14 kPa, the examination will be repeated 4 weeks later (at an unscheduled visit). A liver biopsy may be considered in order to confirm the diagnosis of cirrhosis, if the repeat FibroScan value is confirmed ≥14 kPa, and associated with a platelet count <150 000/mm^3 and at least 1 elevated serum marker of fibrosis indicative of cirrhosis (calculated NAFLD fibrosis >0.676 score or reported FIB-4 >2.67). In the case of detection of variceal rupture at endoscopy or of presence of any cirrhosis related event, such as MELD ≥15, hepatic encephalopathy, or ascites, then the liver biopsy will not be required for diagnosis of cirrhosis, but the diagnosed event will have to be adjudicated by the CEC.

If cirrhosis or any event listed in the long-term composite endpoint is diagnosed, the patient will discontinue the study drug and the study and will be followed up as described in Section 5.2.2 and Section 5.2.3.

6.4. SAFETY & EFFICACY DATA REVIEW

An independent DSMB will be established in order to review the progress of the study and to perform a safety data review on a regular basis during the trial to protect patient welfare and preserve study integrity. The DSMB will also review the interim analysis results and provide final recommendations regarding trial termination due to futility and adjustment of the target number of primary events. A detailed description of the interim analysis procedures and decision-making process will be provided in the DSMB Charter.

The DSMB will consist of at least 5 experienced physicians (1 endocrinologist, 1 cardiologist, 1 hepatologist, 1 oncologist, and 1 nephrologist) and 1 statistician, all of whom will be independent of the participants in the study. The DSMB Charter will define the role, responsibilities, rules, and tasks of the DSMB.

6.5. CLINICAL EVENT COMMITTEE

The CEC will conduct adjudication of all disease progression events included in the primary composite efficacy long-term endpoint (Section 1.9.2, except for histological cirrhosis), all DILI events, and all major cardiovascular events as defined in the CEC charter. The CEC assessment and adjudication will occur in a blinded, consistent, and unbiased manner throughout the course of a study to determine whether the endpoints meet the protocol-specified criteria.

The CEC will be comprised of 2 hepatologists, 2 cardiologists, and 1 endocrinologist, all of whom will be independent of the participants in the study.

6.6. GUIDANCE FOR INVESTIGATORS

6.6.1. Summary of safety data

The safety and tolerability of elafibranor were confirmed in Phase I and Phase II studies.

A Phase I program to assess the safety and tolerability, as well as the PK profile, of elafibranor has been conducted through 12 clinical trials, 1 of which is still ongoing. A total of 621 volunteers were randomized in these studies performed in Phase I centers, including 549 healthy lean subjects, 60 overweight or obese subjects, and 12 patients with type 2 diabetes.

A Phase II program was initiated to assess the safety and efficacy profile of elafibranor in patients suffering from cardiometabolic disorders. To date, 5 Phase IIa pilot trials have been completed in which 297 patients were randomized. A Phase IIb trial has been completed, and evaluated the efficacy and safety of elafibranor 80 mg and 120 mg on steatohepatitis in 274 patients with NASH.

Of the 69 SAEs that have been reported cumulatively in the clinical development program, 48 occurred with elafibranor, 13 with placebo, and 8 prior to administration of study medication. For all SAEs, the treatment code has been broken (end of study unblinding).

Of the 48 SAEs that occurred with elafibranor, only 9 were considered as having a reasonable possibility of relationship to elafibranor by the investigators (serious adverse reaction). They consisted of:

- Atrial fibrillation in a patient with history of arterial hypertension and suspected chronic coronary disease treated with elafibranor 80 mg
- Acute cholecystitis and pancreatitis that occurred in a patient on the second day of drug administration of elafibranor 80 mg
- Spontaneous abortion in a pregnant patient treated for 6 months with elafibranor 80 mg
- Ataxia, tremor and fasciculations in a patient treated for 51 weeks with elafibranor 80 mg
- Acute pancreatitis that occurred after 7 weeks of treatment in a patient treated with elafibranor 120 mg.
- Parkinson's disease in a patient treated for 12 months with elafibranor 120 mg, aged 76 years (in the risk group for Parkinson's disease, and with a family history of Parkinson's disease).

For 3 of the cases (atrial fibrillation, acute cholecystitis and pancreatitis, and Parkinson's disease) after later investigations, given the medical history of the patients or the time of occurrence of the event, relationship to elafibranor was judged as "no reasonable possibility" by the Sponsor.

All adverse reactions (adverse events reported by investigators as possibly related or related to study drug) reported in more than 1% of patients treated with elafibranor in clinical studies with repeated doses of at least 80 mg elafibranor per day are summarized in Table 3.

Table 3: Overview of the common nonserious adverse reactions (>1% of patients treated with elafibranor) by system organ class (SOC) reported in completed elafibranor clinical studies with repeated administration of elafibranor (at least 14 days) from 80 mg/day up to 300 mg/day (MTD)

System Organ Class	Adverse Reaction	Severity	Frequency
Gastrointestinal disorders	Nausea	Mild to severe	4.4%
	Diarrhea	Mild to moderate	3.3%
	Vomiting	Mild to moderate	1.6%
General disorders and administration site conditions	Fatigue	Mild to moderate	1.9%
	Asthenia	Mild to moderate	1.1%
Investigations	Hepatic enzymes increased (mainly transaminases)	Mild to severe	1.8%
	Blood creatine phosphokinase increased	Mild to moderate	1.1%
Musculoskeletal and connective tissue disorders	Myalgia	Mild to severe	1.6%
Metabolism & nutrition disorders	Decrease appetite	Mild to severe	1.6%
Renal and urinary disorders	Renal failure/impairment	Mild to moderate	1.2%
Vascular disorders	Hot flush	Mild to moderate	1.2%

Among the non-serious adverse reactions, the most frequent were gastro-intestinal disorders and general disorders. The first ones consisted mostly of nausea, diarrhea, and vomiting. For general disorders, the main symptoms were fatigue or asthenia. These are considered common and expected.

Other non-serious adverse reactions reported in more than 1% of patients concerned changes in biological parameters such as liver enzymes increase (mainly AT), CPK elevation, or increase of creatinine (reported by investigators as renal failure and/or impairment due to the calculation of creatinine clearance by MDRD based on creatinine). Myalgia, decrease of appetite and hot flush were also reported in more than 1% of patients but remain limited.

Regarding specific monitoring, although no signal for increase in CPK has been observed in the clinical trials, given the known effects of PPARα agonists on the increase of CPK enzyme, this parameter is monitored in clinical trials. For this reason, it is recommended that investigators review these lab results in the course of clinical trials.

Other known effects of PPARα agonists include the increase of creatinine, which was observed in our phase IIa and IIb trials, in a range of 5-10%. This increase was reversible at end of treatment. This should also be monitored in clinical trials.

Liver enzymes will also be monitored in clinical trials, with specific attention paid to DILI.

Based on the findings of nonclinical reproductive and developmental toxicity studies performed to date, and in the absence of human pregnancy data, elafibranor may be classed in the "Possible human teratogenicity/fetotoxicity in early pregnancy" risk category according to the Clinical Trial Facilitation Group (CTFG) document Recommendations related to contraception and pregnancy testing in clinical trials (September 2014).

As such, all clinical trials with elafibranor including WOCBP request a negative pregnancy test before Randomization, with effective contraceptive measures throughout the study. It is recommended to maintain the contraception up to 1 month after end of treatment. Pregnancy tests should be repeated as stated in each study protocol. In the absence of a clinical pharmacokinetic interaction study between elafibranor and contraceptive steroids, the exclusive use of hormonal contraceptive methods during clinical trials should be avoided, and they should be accompanied by barrier methods.

6.6.2. Safety data conclusion

Based on the cumulative experience gathered to date, gastro-intestinal disorders such as nausea, diarrhea and vomiting, and asthenia or fatigue are considered common and expected adverse reactions reasonably associated with elafibranor. Most of them are of mild to moderate intensity. As previously, laboratory increases of serum creatinine or CPK should be monitored throughout clinical trials as this has been observed in Phase II trials, and is a known PPARα agonist effect. Elevation of AT will be monitored as well as DILI. In the absence of human pregnancy data, double contraception should be maintained for women

of childbearing potential participating in clinical trials with elafibranor treatment, up to 1 month after end of study treatment.

6.6.3. Benefit/risk assessment

Numerous Phase I and Phase IIa clinical studies have provided data that support the therapeutic potential of elafibranor in metabolic diseases including NASH. Moreover, the Phase IIb trial demonstrated the efficacy of elafibranor at the therapeutic dose of 120 mg on a clinically meaningful primary endpoint, resolution of histological NASH without worsening of fibrosis, in patients with active disease (NAS ≥4). While the trial was short and not designed for antifibrotic endpoints, it nonetheless showed that elafibranor, at 120 mg daily, improved fibrosis indirectly through the resolution of NASH. Importantly, elafibranor 120 mg concomitantly improved the cardiometabolic risk profile of the patients by decreasing plasma triglycerides, total and LDL-cholesterol, increasing HDL-cholesterol, and improving inflammation, insulin resistance, and glucose homeostasis. Together these results position elafibranor as a drug candidate to treat NASH with the objective to block fibrosis evolution and ultimately avoid long term liver outcomes while reducing cardiovascular risk.

Moreover, clinical studies completed to date have not raised any major safety concerns associated with elafibranor treatment, thus providing a favorable efficacy/safety profile for the drug candidate.

Despite this favorable benefit-risk profile, an independent Data Safety Monitoring Board (DSMB) is to be established in order to review the safety of the treatment during the trial in an unblinded manner, to protect patient welfare and preserve study integrity. The safety assessments will be performed on a regular basis, every 6 months after Randomization of the first patient. The DSMB will consist of 5 experienced physicians (1 endocrinologist, 1 cardiologist, 1 hepatologist, 1 oncologist, and 1 nephrologist) and 1 statistician, all independent of the participants in the study.

In addition, throughout the study, patients will benefit from close safety monitoring including assessment of many safety parameters and follow-up of the disease progression, mainly through noninvasive measures including FibroScan.

7. TREATMENTS

7.1. DESCRIPTION OF STUDY MEDICATIONS

Elafibranor (propanoic acid, 2-[2,6-dimethyl-4-[3-[4-(methylthio)phenyl]-3-oxo-1(E)-propenyl] phenoxy]-2-methylpropanoic acid) will be supplied as 120 mg white to off-white round coated tablets with no printed inscription. The tablet contains elafibranor and inactive ingredients [redacted]

Placebo to match elafibranor 120 mg will be provided as a white to off-white round coated tablet with no printed inscription.

For additional information see Investigator's Brochure.

7.2. PACKAGING AND LABELING

7.2.1. Packaging

Elafibranor/placebo:

The primary packaging is composed of opaque polyamide/aluminum/PVC complex and aluminum foil blisters. This has been shown to be a suitable primary packaging for tablets.

Blisters, containing 8 tablets each, will be packed in child proof wallets.

Each childproof wallet will contain 4 blisters. Three wallets will be packaged inside a carton.

7.2.2. Labeling

All labels for study drugs meet all applicable requirements of the US Food and Drug Administration (FDA) and the EU annex 13 of Good Manufacturing Practices: Manufacture of Investigational Medicinal Products (February 2010) and /or other local regulations, as applicable.

Distribution of study drug will be performed according to the Good Distribution Practices.

Product cartons will be labeled with the protocol number, Sponsor's name and address, description of contents, storage conditions, expiry date, dosage instructions, and any other applicable items required by national and regional guidelines/regulations. The label will contain the statements "For clinical trial use only" or other similar/appropriate statements as well as the following instructions "Please return empty packaging and unused products to your doctor at your next visit." Details of carton and wallet labels are detailed in APPENDIX V: Product carton and wallet labeling

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7.3. DOSAGE AND ADMINISTRATION OF ELAFIBRANOR AND PLACEBO

Patients will be informed to take one tablet per day of elafibranor 120 mg or placebo orally before breakfast with a glass of water each morning.

7.4. METHOD OF ASSIGNING PATIENT TO TREATMENT GROUP

Upon screening of the first patient, the IXRS system will immediately forward the information to the Drug Distribution Center which will be responsible to send one of several blocks of treatment packages (containing 96 tablets to last approximately 3 months) allocated to the site. The pharmacy will acknowledge receipt of the study drug in the IXRS.

An e-mail, confirming that the patient has been screened, will be sent to the Investigator, [redacted] and to the Sponsor.

After having received the liver biopsy results as well as the SV1 laboratory results (SB1) (or when applicable, results of any retesting performed), and if the patient fulfills all criteria to enter the treatment period, the Investigator will register the patient in the IXRS to randomize him/her.

The IXRS will check if the Investigator is authorized to use the system (identification number and access code) and will ask some questions to check the patient eligibility. The IXRS will then allocate the patient to a treatment group (elafibranor 120 mg or placebo) through a patient number (with 9 digits), as described in Section 3.2.

A specific IXRS procedure manual will be provided to the pharmacy.

The randomization list will be generated by the IXRS partner and will be kept in blinding condition to the study participants until the Blind-Review Meeting and the Sponsor authorization to unblind the trial.

7.5. STORAGE CONDITIONS

Elafibranor and placebo should be stored between +15°C and +25°C (59°F and 77°F). Storage conditions are specified on the label.

7.6. DISPENSING OF TREATMENT

Each site will have a resupply strategy within the IXRS to determine the supply of study drugs sent to each site. Initial site shipments will be shipped at a static value defined in the supply strategy. Following randomization of a patient IXRS will project for the amount of study drug required for future visits and ensure the study drug is at site for the visits occurring. The IXRS will continue to project study drug requirements per patient until an event occurs which stops the projections for that patient.

The Investigator will register the patient's visit in the IXRS who will allocate to the patient a treatment package for approximately 3 months (96 tablets) in the First Treatment Period and for approximately 6 months (192 tablets) in the LTTP. An e-mail, confirming the registration, will be sent to the Investigator and to the Sponsor.

The treatment package will include a carton with 3 wallets of 4 blisters for the First Treatment Period and 2 cartons with 3 wallets of 4 blisters in the LTTP.

Each randomized patient will be given, from V1 and at every following visit, the study medication containing the adequate number of wallets to cover the drug administration for the period between visits. The time between visits will be 12 weeks ± 1 week (to a maximum of 96 days) during the First Treatment Period and 24 weeks ± 2 weeks (to a maximum of 192 days) between visits in the LTTP, which correspond to the number of tablets provided to the patient at each visit.

7.7. TREATMENT REPLACEMENT

A specific IXRS procedure manual will be provided to the Investigator and will detail the procedure in case of need of treatment replacement.

7.8. PROCEDURE FOR BLINDING

The Investigator, patient, and study personnel will be blinded to the treatment.

Identification numbers will be assigned to a patient at the Screening Visit. The number will also be reported in the eCRF. Upon completion of the Screening Visit(s), eligible patients will be randomly assigned to active treatment (elafibranor 120 mg) or placebo at the first visit of the First Treatment Period (V1).

7.9. PROCEDURE FOR UNBLINDING

The randomization code may be broken by the Investigator when urgent action is required for the clinical management of the patient. For each patient, the list of treatment numbers allocated to the patient will be stored in the IXRS. The Investigator will be able to unblind any treatment carton that was dispensed to the patient by connecting to the IXRS (**24-hour & 7-day access**) and entering their identification number and access code. A back-up phone Interactive Response Technology (IRT) module will also be available should the site be unable to access the internet. The IXRS will verify the authorization to unblind the entered treatment carton and the screen will then display the treatment group, when completed, a blinded confirmatory e-mail will be sent to the Investigator and the Sponsor.

The reason for unblinding should be clearly and fully documented by the Investigator.

7.10. STUDY DRUG COMPLIANCE

From V2 and at every following visit while the patient is being treated with study drug, the patient will be directed to bring back all used and unused cartons and blisters. Compliance will be checked by the Investigator during those visits and registered in the eCRF.

If treatment is interrupted, whatever the cause, duration and reason of the interruption should be documented.

7.11. TREATMENT ACCOUNTABILITY, RETRIEVAL AND DESTRUCTION.

The Investigator or pharmacist will acknowledge receipt for each study treatment on the day of receipt. A drug accountability record should be maintained by the person responsible for dispensing the trial medication to the patient.

All partially used or unused treatments will be inventoried by the monitor during and at the conclusion of the study.

On Sponsor request, the Drug Distribution Center will organize the retrieval of all treatments (used or unused) and will proceed to their destruction only after the Sponsor provides written authorization.

If the site has an appropriate Standard Operating Procedure (SOP) for drug destruction, the site may destroy used and unused study drugs in accordance with the site SOP and always after the drug accountability has been performed by the monitor.

If drug is destroyed in the site, the Investigator must maintain accurate records for treatment cartons destroyed recording:

- Treatment carton (kit) number (see APPENDIX V: Product carton and wallet labeling)
- Quantity destroyed
- Method of destruction
- Person who disposed the drug.

7.12. OTHER MEDICATION

7.12.1. Handling of concomitant medication

In a general manner, patients should be discouraged from starting any new medication without consulting the Investigator unless the new medication is required for emergency purpose. In the same way, any qualitative or quantitative change in concomitant therapy should be avoided, when possible (see table II, APPENDIX III: Permitted/non-permitted medication). In the event that it becomes necessary during the study, this should be recorded by the Investigator in the eCRF (including concomitant medications taken within 6 months prior to Screening) and information should be communicated to the Medical Monitor in

order to evaluate the risk of DDIs. This includes drugs used on a chronic as well as on an "as needed" basis.

7.12.2. Non-permitted medication (see Table I, APPENDIX III: Permitted/non-permitted medication)

The following medications are not allowed within the timeframe given in APPENDIX III: Permitted/non-permitted medication):

- Thiazoledinediones (glitazones [pioglitazone & rosiglitazone])
- Fibrates
- Corticosteroids (parenteral & oral chronic administration only)
- Amiodarone
- Tamoxifen
- Methotrexate
- Indomethacin.

The following medications are not allowed to be initiated prior to diagnostic liver biopsy and up to 72 weeks of treatment (see APPENDIX III: Permitted/non-permitted medication):

- GLP-1 agonist
- SGLT2 inhibitors.

If it is identified that these non-permitted drugs have been administered to a patient within the excluded timeframes, the site will discuss the continuation of the patient with the Medical Monitors of the study.

7.12.3. Permitted medication under condition (see Table II, APPENDIX III: Permitted/non-permitted medication)

The following medications are permitted under the condition of steady dosage prior to Screening (dose changes are allowed after Randomization if judged necessary by the physician):

- Statins, ezetimibe, and other nonfibrate lipid lowering medications, provided the dosage is kept stable for at least 2 months prior to Screening.

The following medications are permitted under the condition of stable dose from at least 6 months prior to diagnostic liver biopsy (dose changes should be avoided up to EOT):

- Vitamin E >400 IU/day
- PUFAs >2 g/day
- Ursodeoxycholic acid.

The following medications are permitted under the condition of no qualitative change (i.e., implementation of a new antidiabetic drug) in the 6 months prior to diagnostic liver biopsy and up to Randomization:

- Insulin
- Sulfonylureas
- Metformin
- Gliptins
- SGLT2-inhibitors
- GLP-1 agonists.

Dose changes are allowed for these medications, except for GLP-1 agonists, which must be on stable dose in the 6 months prior to diagnostic liver biopsy and up to randomization.

In addition, no initiation of SGLT2-inhibitors and GLP-1 agonists is allowed from at least 6 months prior to the diagnostic liver biopsy up to 72 week of treatment (V7).

Patients on sulfonylureas and insulin are recommended to self-monitor blood glucose.

7.12.4. Permitted medication

Any medications other than those listed above are permitted. However, the dosage of a current medication for a chronic disease should remain unchanged as far as possible in order to reduce the risk of unknown DDIs.

In the event that additional concomitant therapy becomes necessary during the study, this should be recorded by the Investigator in the eCRF. This includes drugs used on a chronic as well as on an "as-needed" basis. Patients should be discouraged from starting any new medication without consulting the Investigator unless the new medication is required for emergency purpose.

8. ADVERSE EVENT AND TOXICITY MANAGEMENT

8.1. DEFINITIONS

8.1.1. Adverse events

Any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical (investigational) product and which does not necessarily have to have a causal relationship with this treatment will be considered as an AE. The term AE is synonymous with the term "adverse experience" as used by the FDA.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding or physiological observation, for example), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal product.

Examples of AE include (but are not limited to): abnormal test findings; clinically significant symptoms and signs; changes in physical examination findings; hypersensitivity; progression/worsening of pre-existing condition or underlying disease; recurrence of a pre-existing condition; lack of effect, complication, and termination of pregnancy.

Additionally, they may include the signs or symptoms resulting from: drug overdose, drug withdrawal, drug abuse, drug misuse, drug interactions, drug dependency, extravasation, exposure in utero.

The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

- Test result is associated with accompanying symptoms
- Test result requires additional diagnostic testing or medical/surgical intervention
- Test result leads to a change in trial dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy
- Test result is considered to be an AE by the Investigator or Sponsor.

Repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

An AE does not include the following:

- Medical or surgical procedures performed; the condition that leads to the procedure may be an AE if applicable
- Pre-existing disease, condition or laboratory abnormalities present or detected before the Screening Visit that do not worsen
- Overdose without clinical sequelae

- Any medical condition, or clinically significant laboratory abnormality with an onset before the consent form is signed. Such as medical condition is considered to be pre-existing and should be documented on the medical history of the eCRF
- Uncomplicated pregnancy
- An induced elective abortion to terminate a pregnancy without medical reason
- Events that are identified as efficacy endpoints for the long-term evaluation (described in Section 1.9.2) should not be reported as AE.

The questions concerning whether the condition existed before the start of the active phase of the study and whether it has increased in severity and/or frequency will be used to determine whether an event is a treatment-emergent AE. An AE is considered to be treatment emergent if (1) it is not present when the active phase of the study begins and is not a chronic condition that is part of the patient's medical history, or (2) it is present at the start of the active phase of the study or as part of the patient's medical history, but the severity or frequency increases during the active phase. The active phase of the study begins at the time of the first dose of the study drug. The active phase of the study ends at the last study visit.

8.1.2. Serious adverse events

A SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (see Section 8.1.2.1)
- Requires inpatient hospitalization or prolongation of existing hospitalization (see Section 8.1.2.2)
- Results in persistent or significant disability/incapacity (see Section 8.1.2.3)
- Is a congenital anomaly/birth defect (including fetal malformations associated with spontaneous abortions or elective abortions)
- Is another medically important condition (see Section 8.1.2.4).

In addition, any illnesses reported before starting active treatment or AE meeting the criteria of seriousness (as defined above) and considered to be possibly related (according to the Investigator) to any study-specific procedure (e.g., laboratory testing procedure, liver biopsy) must be reported as an SAE.

8.1.2.1. Life-threatening adverse events

- A life-threatening AE in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

8.1.2.2. *Inpatient or prolonged hospitalization*

An inpatient hospitalization or prolongation of a hospitalization means that the patient stays overnight in the hospital. An overnight stay is defined by hospitalization of 24 hours. Visits to the emergency room will

not be considered hospital admission. Pre-planned hospital stays or hospital stays for nonmedical social reasons will not be considered as hospitalization, for example:

- Hospitalization or prolongation of hospitalization is needed for a procedure required by the protocol. Day or night survey visits for biopsy or surgery required by the protocol are not considered serious.
- Hospitalization or prolongation of hospitalization is part of a routine procedure followed by the study center (e.g., stent removal after surgery). This should be recorded in the study file.
- Hospitalization for survey visits or annual physicals fall in the same category.
- Hospitalization planned before the start of the study for a pre-existing condition that has not worsened does not constitute an SAE (e.g., elective hospitalization for a total knee replacement due to a pre-existing condition of osteoarthritis of the knee that has not worsened during the study).

8.1.2.3. Significant or incapacitating disability

Only a persistent or significant or incapacitating disability is intended. This item refers to a substantial disruption of a person's ability to conduct normal life functions. Thus, disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma.

8.1.2.4. Medically important conditions

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

Examples of such events are:

- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias or convulsions that do not result in hospitalization
- Development of drug dependency or drug abuse.

8.1.3. Clarification on serious adverse events:

- Events that are identified as primary efficacy endpoints for the long-term evaluation should not be included as an AE.
- Death is an outcome of an AE, not an AE in itself.
- An SAE may occur even if the patient was not being treated with the investigational medicinal product at the occurrence of the event.

- Life-threatening means that patient is at immediate risk of death. This does not include an event that might have led to death if it had occurred with greater severity.
- Complications that occur during hospitalizations are AEs. If a complication prolongs the hospitalization, it is a SAE.
- Patient hospitalization means that the patient stays overnight in the hospital. Pre-planned hospital stays or hospital stays for nonmedical social reasons will not be considered as hospitalization.
- A procedure for protocol/disease-related investigations (e.g., biopsy) should not be reported as SAE. Hospitalization or prolonged hospitalization for a complication of such procedures should be reported as SAE.

8.1.4. Adverse drug reaction

An adverse drug reaction (ADR) is defined as a response to a medicinal product which is noxious and unintended and that is considered casually related to an investigational medicinal product. A serious ADR (SADR) is an ADR which meets the seriousness criteria.

8.1.5. Unexpected adverse event

Expectedness is assessed by the Sponsor. An unexpected AE is defined as an event that has a nature of severity or specificity that is not consistent with the applicable Investigator Brochure or that is symptomatically and pathophysiologically related to a known toxicity but differs because of a greater severity or specificity.

"Unexpected" refers to an ADR that has not been previously observed and reported rather than an event that has not been anticipated based on the properties of the drug.

8.2. ASSESSMENTS

The Investigator will establish whether or not any AE have occurred at each visit from the date of consent. The patient will be questioned in a general manner to determine specific symptoms without offering the patient any suggestion.

8.2.1. Intensity assessment

The intensity of the AE will be graded as follows:

- **Mild**: Awareness of signs or symptoms, but easily tolerated and are of minor irritant type causing no loss of time from normal activities. Symptoms do not require therapy or a medical evaluation; signs and symptoms are transient.
- **Moderate**: Events introduce a low level of inconvenience or concern to the participant and may interfere with daily activities, but are usually improved by simple therapeutic measures; moderate experiences may cause some interference with functioning.

- **Severe**: Events interrupt the participant's normal daily activities and generally require systemic drug therapy or other treatment; they are usually incapacitating.

8.2.2. Relation to the study treatment

The Investigator will make a clinical and scientific judgment regarding whether or not the AE was related to study treatment. The Investigator will evaluate any changes in laboratory values, make a determination as to whether or not the change is clinically important, and whether or not the changes were related to study drug. However, even if the Investigator feels there is no relationship to the study drug, the AE or clinically significant laboratory abnormality must be recorded in the eCRF.

The Investigator will record the relation to the study treatment according to the following causality terms:

- **Related:** the AE follows a reasonable temporal sequence from the time of drug administration and it cannot be explained by the patient's clinical state or the study procedures/conditions. The AE abates upon discontinuation of the study drug and reappears when the study drug is introduced.
- **Possibly related:** the AE follows a reasonable temporal sequence from the time of drug administration, but could have been produced by the patient's clinical state or the study procedures/conditions.
- **Unlikely related:** the temporal association between the AE and the study drug is such that the study drug is not likely to have any reasonable association with the AE. The relationship is not likely because of other plausible explanations.
- **Not related:** the AE must definitely be caused by the patient's clinical state or the study procedure/conditions. A reasonable explanation must be given, e.g., no investigational product taken, preplanned elective medical intervention, or incompatible temporal relationship.
- **Not assessable**: the report suggesting an adverse reaction cannot be judged because information is insufficient or contradictory and data cannot be supplemented or verified.

8.2.3. Action taken and outcome

The Investigator will record the action taken with drug and outcome of the event for each AE according to the following:

<u>Action taken with investigational drug</u>

- Drug permanently withdrawn – in case a patient is permanently withdrawn from the study drug
- Drug temporarily withdrawn – in case the study drug is temporarily withdrawn
- Dose not changed – in case no action is taken regarding the study drug
- Unknown
- Not applicable – an AE started before initiation of treatment with study drug, the treatment had been completed prior to reaction/event, or the patient has died.

Outcome

- Recovered/resolved
- Recovering/resolving
- Not recovered/not resolved
- Recovered/resolved with sequelae
- Fatal
- Unknown.

Note: In case of irreversible congenital anomalies the choice not recovered/not resolved should be used. "Fatal" should be used when death is possibly related to the reaction/event.

8.3. REPORTING

8.3.1. Reporting an adverse event

All AEs regardless of seriousness or relationship to study drug, including those occurring during the Screening Period, are to be recorded on the corresponding page(s) of the eCRF and in the patient's medical record from the ICF signature until study end for each patient. Whenever possible, symptoms should be grouped as a single syndrome or diagnosis. The Investigator should specify the date of onset, maximal intensity, action taken with respect to study drug, corrective therapy given, outcome, and his/her opinion as to whether there is a reasonable possibility that the AE was caused by the study drug.

Adverse event reporting begins from signature of the patient ICF at the first Screening Visit and ends at study end for each patient.

8.3.2. Reporting a serious adverse event

Serious AE reporting begins from signature of the patient ICF and ends at study end for each patient.

Any SAE that is brought to the attention of the Investigator at any time after the reporting period and which is considered by him/her to be caused by the study drug within a reasonable possibility, should be reported.

Any of the portal hypertension/cirrhosis related events described in Section 2.1.1 that are identified as potential primary efficacy endpoints for long-term evaluation will NOT be reported as SAEs unless it is determined by the adjudication committee that the event does not meet the predefined criteria for an endpoint. Events that are identified as potential primary efficacy endpoints for long-term evaluation that are not confirmed by adjudication will be reported as described with the start of the reporting time window being the time of negative adjudication decision.

Investigators must notify, by fax or e-mail, the Sponsor designated representative [redacted] of all SAEs **IMMEDIATELY (within 24 hours of the Investigator becoming aware of the event).**

ANY SERIOUS ADVERSE EVENTS, WHETHER OR NOT RELATED TO THE STUDY DRUG, MUST BE REPORTED IMMEDIATELY (WITHIN 24 HOURS) TO [redacted] AT THE FOLLOWING FAX NUMBERS:

FAX numbers: [redacted]

Contact Person: [redacted]

E-mail: [redacted]

All SAEs independent of the circumstances or suspected cause must be reported in ENGLISH on a SAE Form. The SAE Form should include a clearly written narrative describing signs, symptoms, and treatment of the event, diagnostic procedures, as well as any relevant laboratory data and any sequelae, in order to allow a complete medical assessment of the case and independent determination of the possible causality.

The Investigator is also required to submit follow-up SAE reports to [redacted] within 24 hours of becoming aware of additional information such as diagnosis, outcome, causality assessment, results of specific investigations, and any new significant information that has not been previously reported.

It is critical that the information provided on the initial or follow-up SAE Form matches the information recorded in the source documents and the eCRF for the same event.

Copies of additional laboratory tests, consultation reports, postmortem reports, hospital case reports, autopsy reports, and other documents should be sent when requested and applicable. All provided reports must be anonymized.

Follow-up reports relative to the patient's subsequent course must be submitted to [redacted] until the event has subsided or, in case of permanent impairment, until the condition stabilizes.

The Sponsor or its designated representative will report all the relevant safety information to the concerned Competent Authorities and to the Independent Ethics Committee(s) (IRB/IEC) concerned according to the country-specific requirements.

Investigator must fulfill his/her regulatory obligations to the Regulatory Authorities and/or to the Ethics Committee in accordance with local regulations.

Depending on local regulations in different regions and countries, the Sponsor or designated clinical research organization (CRO) may be required to expedite report to the Regulatory Authorities for:

- SAEs (including events related to study procedures)
- SADRs
- Suspected unexpected serious adverse reactions (SUSARs)

Each SAE report received from the Investigators will be evaluated by the designated CRO for pharmacovigilance who will assess the seriousness of the event. Each SAE report will be evaluated by the Sponsor and/or his designees who will assess the relationship to study procedure or study treatment and the expectedness of the event. Expectedness will be assessed using the reference safety information included in the Investigator Brochure.

Any unexpected safety issue that changes the risk benefit analysis and is likely to have an impact on the patients who have participated in the trial will be reported by the Sponsor as soon as possible to the Competent Authority(ies) concerned together with proposed actions.

8.3.3. Follow-up

The Investigator should take all appropriate measures to ensure the safety of the patients, notably he/she should follow up the outcome of any AE until the return to normal or until stabilization of the patient's condition.

The patient must be followed up until clinical recovery is complete and laboratory results have returned to normal, or until progression has been stabilized. This may imply that follow-up will continue after the patient has left the study and that additional investigations may be requested by the Sponsor. This information should be documented in the patient's medical records.

8.4. POST STUDY REPORTING REQUIREMENTS

Any SAEs and deaths that occur within 30 days of the last dose of the study drug, regardless of causality, should be reported.

Any SAE that is brought to the attention of the Investigator at any time after the reporting period and which is considered by him/her to be caused by the study drug within a reasonable possibility, should be reported.

8.5. CLINICAL LABORATORY ABNORMALITIES AND OTHER ABNORMAL ASSESSMENTS AS ADVERSE EVENTS OR SERIOUS ADVERSE EVENTS

Laboratory abnormalities are not necessarily recorded as AEs or SAEs. However, laboratory abnormalities that are considered clinically relevant by the Investigator must be recorded as an AE or SAE as applicable.

8.6. SPECIAL SITUATION REPORTS

Special situations reports include pregnancy reports, reports of medication error, abuse, misuse or overdose, and reports associated with product complaints.

8.6.1. Pregnancy

In case of pregnancy a communication will be sent by the Investigator to [redacted] by faxing a completed pregnancy form within 24 hours of his/her knowledge of the pregnancy.

Pregnancies of females partners of male patients exposed to study medication should also be reported to [redacted] using the corresponding pregnancy form, provided that pregnant female partners have signed an informed consent.

Female patients must be instructed to discontinue the study drug immediately and inform the Investigator as soon as possible once they are aware of being pregnant or suspect that they are pregnant during the study or within 30 days of the last dose of the study drug.

Female patients will be requested, as part of the general ICF, to provide informed consent to allow reasonable attempts to be made to obtain information on any possible medicinal product exposure to an embryo or fetus and to follow up on the outcome of the pregnancy.

The Investigator will contact the patient at the expected time of delivery for follow-up. If the outcome of pregnancy meets the criteria for immediate classification of an SAE (e.g., spontaneous or therapeutic abortion, stillbirth, neonatal death, congenital anomaly, birth defect), the Investigator should follow the procedure for reporting SAEs as detailed in Section 8.3.2.

The pregnancy itself is not considered an AE.

8.6.2. Medication error

Medication error is defined as an unintentional error in the prescribing, dispensing, or administration of a medicinal product while in the control of the healthcare professional, patient, or consumer. All medication errors will be documented in the eCRF and, in case of any potential risk to patient safety, would be reported as appropriate (see Section 8.3).

8.6.3. Misuse

This refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the authorized product information and will be reported in the eCRF. All misuse will be documented in the eCRF and, in case of any potential risk to patient safety, would be reported as appropriate (see Section 8.3).

8.6.4. Overdose

This refers to the administration of a quantity of a medicinal product given per administration or cumulatively, which is above the maximum recommended dose according to the authorized product information (see Section 8.1.1 and Section 8.3.1). Clinical judgment should always be applied.

8.6.5. Abuse

This corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

9. STATISTICAL METHODS AND DATA ANALYSIS

This section is an overview of the key elements of the statistical analysis for this study. Further details on statistical reporting and analyses will be contained in a separate statistical analysis plan (SAP). This SAP may be revised during the study only to accommodate protocol amendments and to make changes to adapt to unexpected issues in study execution and data collection that could affect planned analyses. In all circumstances, a final SAP should be issued prior to database lock and treatment unblinding. The first approved version of the SAP should be available within 3 months of first patient randomized and before the first DSMB meeting.

The main analyses will be based on patients with fibrosis stage F2 and F3. The summaries will be repeated in an exploratory manner with the inclusion of patients with fibrosis stage F1.

9.1. RANDOMIZATION AND TREATMENT ASSIGNMENT

Random allocation will be made to the 2 treatment groups (elafibranor and placebo) in a 2:1 ratio basis and stratified by the following factors:

- Type 2 diabetes (yes, no)
- Gender (male, female) (with a capping of women to 40%)
- Fibrosis stage (F1, F2, F3) (capped to 202 F1 patients).

Details on the randomization process are in Section 3.2.

9.2. ENDPOINTS

9.2.1. Surrogate endpoint - resolution of NASH

The first surrogate endpoint for this study is resolution of NASH without worsening of fibrosis after 72 weeks of treatment. Resolution of NASH is defined as the disappearance of ballooning (i.e., grade 0) and disappearance or persistence of minimal lobular inflammation (i.e., grade 0 or 1) with an overall pattern of injury not qualifying for steatohepatitis. Worsening of fibrosis is evaluated using NASH CRN fibrosis staging system and defined as progression of at least 1 stage. This surrogate endpoint will be formally assessed at the time of the surrogate efficacy analysis when at least 1023 of the F2 to F3 patients complete the 72 week treatment period or discontinue early from the study (see Section 9.8.1 for details). An additional exploratory analysis of this endpoint will take place at the time of the final analysis.

9.2.2. Long-term endpoint – time to clinical event/death

The long term endpoint of clinical outcomes is a composite endpoint composed of death due to any cause, liver cirrhosis, and the full list of portal hypertension/cirrhosis related events:

- Liver transplantation
- MELD score ≥15

- HCC
- the onset of:
    - variceal bleed
    - hepatic encephalopathy
    - spontaneous bacterial peritonitis
    - ascites
    - hepatorenal syndrome
    - hepatopulmonary syndrome
    - chronic gastrointestinal blood loss due to portal hypertensive gastropathy (provided that these lead to hospitalization or transfusion).

The final analysis will be performed when 456 patients experience an event listed above. This is expected to occur approximately 72 months after the first patient is randomized.

9.2.3. Key Secondary Endpoint

The key secondary endpoint is:

- Percentage of patients with improvement of fibrosis of at least 1 stage according to NASH CRN scoring at 72 weeks.

This key secondary endpoint will be assessed at the time of the surrogate endpoint analysis (at least 1023 patients with fibrosis stage F2 and F3) for the resolution of NASH without worsening of fibrosis endpoint.

9.2.4. Other Secondary Endpoints

The other secondary endpoints are:

- To assess histological changes after 72 weeks of treatment and follow-up biopsy on the following endpoints:
    - percentage of patients with resolution of NASH without worsening of fibrosis (follow-up biopsy)
    - percentage of patients with improvement of fibrosis of at least 1 stage according to NASH CRN scoring
    - percentage of patients with at least 1 point improvement in histological scores (NASH CRN scoring: total NAS, steatosis, hepatic ballooning, lobular inflammation), fibrosis (NAFLD Ishak scoring system), or portal inflammation
    - percentage of patients improvement of NAS of at least 2 points
    - percentage of patients with at least a 1 point improvement in SAF activity score
    - mean changes in NAS, steatosis, hepatic ballooning, lobular inflammation, portal inflammation, SAF activity score
    - changes in area of fibrosis by morphometry

  - mean changes in fibrosis using NASH CRN and NAFLD Ishak scoring.
- To assess the following endpoints at Week 72 and at the end of the LTTP:
  - changes in liver enzymes and liver markers
  - changes in noninvasive markers of fibrosis and steatosis
  - changes in lipid parameters
  - variation in body weight
  - changes in insulin resistance and glucose homeostasis markers
  - changes in inflammatory markers
  - changes in cardiovascular risk profile as assessed by Framingham scores
  - changes in quality of life (SF-36 questionnaire).
- To assess the onset to:
  - liver cirrhosis
  - death of any cause
  - any portal hypertension or cirrhosis related events
  - cardiovascular events
  - liver-related death events.

9.2.5. Exploratory endpoints

The exploratory endpoint is:

- To constitute a biobank for discovery and validation of biomarkers in NASH.

Details on all endpoints will be given in the SAP.

9.3. ANALYSIS SETS

The following analysis sets will be used in this study:

- Enrolled: all patients who sign informed consent. This set will be used to summarize disposition.
- ITT: all randomized F2 and F3 patients. This set will be used to summarize efficacy. The main analysis of the primary and key secondary endpoints will be based on the ITT.
- Safety set (SS): all randomized F2 and F3 patients who receive at least 1 dose of study drug. This set will be used to summarize safety.
- Per protocol set (PPS): all F2 and F3 patients who receive at least 1 dose of study drug and do not have any important protocol deviations leading to exclusion from the PPS. Important protocol deviations will be defined in the SAP and agreed prior to database lock. Supportive analysis of the primary and key secondary endpoints will be based on the PPS.
- Exploratory F1 cohort: All randomized F1 patients who have taken at least 1 dose of study drug.
- Full Intent-To-Treat Set (FITT): all randomized patients.
- Full Safety Set (FSS): all randomized patients who receive at least 1 dose of study drug.

Patients in the ITT, FITT, PPS, and exploratory F1 cohorts (study population and efficacy data) will analyzed based on randomized treatment. Patients in the SS, FSS, and exploratory F1 cohorts (safety data) will be analyzed based on actual treatment received.

9.4. ANALYSIS OF PRIMARY ENDPOINTS

9.4.1. Resolution of NASH

The null hypothesis for resolution of NASH without worsening of fibrosis is that there is no difference in response rates between the elafibranor and placebo groups. The alternative hypothesis is that there is a difference in response rates between the elafibranor and placebo groups. The null hypothesis will be tested at the two-sided 0.01 alpha level.

The number and percentage of patients with resolution of NASH without worsening of fibrosis at the end of the 72 week treatment period will be summarized by treatment group. The main analysis will be performed using a logistic regression model, with fixed terms for treatment, type 2 diabetes (yes, no), gender (male, female), fibrosis stage (F2, F3) and baseline NAS. The statistical model will be used to calculate the odds ratio (elafibranor/placebo) and 99% confidence interval. The main confirmatory analysis will be performed when at least 1023 F2/F3 patients have completed the 72 week treatment period or discontinued from the study. The main analysis will be based on the ITT. Supportive analysis will be based on the PPS.

Patients with missing data for resolution of NASH without worsening of fibrosis will be treated as a nonresponder for the main analysis. Additional sensitivity analysis using multiple imputations and a pattern mixture model will be performed. Further details will be provided in the SAP.

9.4.2. Long-term endpoints

The null hypothesis is that there is no difference in the hazard ratio between the elafibranor and placebo treatment groups. The alternative hypothesis is that there is a difference in the hazard ratio between the elafibranor and placebo treatment groups. The null hypothesis will be tested at the two-sided 0.04 alpha level.

The data will be analyzed using a Cox proportional hazards model with fixed terms for treatment, type 2 diabetes, gender, fibrosis stage, and baseline NAS. The Cox proportional hazards model will be used to calculate the hazard ratio (elafibranor/placebo) and 96% confidence interval. This will be performed when at least 456 patients experience a clinical event/death. The time to clinical event/death and time to first cardiovascular event death will also analyzed using an unadjusted Cox-proportional hazard's model, log rank test and a nonparametric randomization based analysis of covariance method proposed by Saville and Koch.[36]

The time to clinical event/death will be presented graphically using a Kaplan-Meier curve. The median time to first clinical event/death and 95% confidence interval will also be presented for each treatment group.

Missing data will be censored at the last known date.

The main analysis will be based on the IIT. Supportive analysis will be based on the PPS.

9.5. OTHER STATISTICAL ANALYSIS

9.5.1. Key secondary endpoint

The number and percentage of patients with improvement of fibrosis according to NASH CRN scoring at the end of the 72 week treatment period will be summarized separately by treatment group. The data will be analyzed using a logistic regression model, with fixed terms for treatment, type 2 diabetes, gender, fibrosis stage and baseline NAS by NASH CRN scoring. The analysis will be performed at the time of the surrogate endpoint analysis when at least 1023 of patients with fibrosis stage F2 and F3 have completed the 72 week treatment period or discontinued from the study. The null hypothesis will be tested at the two-sided 0.01 alpha level.

The main analysis will be based on the IIT. Supportive analyses will be based on the PPS.

9.5.2. Other secondary endpoints

All other secondary endpoints will be summarized by treatment group using descriptive statistics. The main analysis will be based on the ITT.

Categorical endpoints will be analyzed using a logistic regression model in the same manner as resolution of NASH without worsening of fibrosis.

Time to event endpoints will be analyzed using the Cox proportional hazard's model in the same manner as time to clinical event/death.

Continuous endpoints will be analyzed using an Analysis of Covariance (ANCOVA) model with fixed terms for treatment, type 2 diabetes, gender, fibrosis stage, and baseline NAS. An unstructured covariance matrix will be used for this analysis. The statistical model will be used to calculate the mean treatment difference and 95% confidence interval. If the data does not meet the required assumptions for parametric tests, the data will be analyzed using a nonparametric analysis of covariance method of Zink and Koch.[37]

Further details will be in the SAP.

9.5.3. Subgroup analyses

Exploratory analyses of the primary and key secondary endpoints will be done for selected subgroups, including, but not limited to, the following:

- Presence of type 2 diabetes (yes, no)
- Gender (male, female)

- Fibrosis (F2, F3)
- Geographic region (North America, Europe, South America, Rest of World)
- Race (Caucasian, Other)
- Ethnicity (Hispanic, not Hispanic)
- Age (<60, ≥60 years).

Forest plots will be generated for each of these endpoints for patients in the ITT population.

9.5.4. Exploratory analyses

Additional exploratory analyses of the efficacy data will be performed on the exploratory F1 cohort.

9.6. STRATEGIES TO CONTROL TYPE I ERROR

The overall type I error for the primary endpoints in this study is two-sided α=0.05. The alpha for the primary endpoints will be split 20%/80%, with two-sided α=0.01 for resolution of NASH and two-sided α=0.04 for time to clinical event/death.

A hierarchical gate-keeping strategy will be used to control for multiplicity for the key secondary endpoint. If the resolution of NASH without worsening of fibrosis endpoint is statistically significant, the key secondary endpoint, improvement of fibrosis according to NASH CRN scoring, will be tested in a confirmatory manner with a two-sided α=0.01.

Statistical testing for all other secondary endpoints will be of exploratory nature.

As this is a single pivotal study that will be used for a regulatory submission, the consistency of the results for the primary and key secondary endpoints will be further explored by population and selected subgroups. In addition, different approaches will be applied for dealing with missing data.

9.7. SAMPLE SIZE CALCULATION

All sample size calculations were done in EAST 6.3.

9.7.1. Resolution of NASH

The following assumptions were made for the sample size calculation for resolution of NASH:

- α=0.01 two-sided
- Randomized patients with no response assessment at Week 72 will be counted as nonresponders
- Pooled variance
- Randomization ratio of 2:1 (elafibranor: placebo)
- 8% response in the control group
- 16.5% response in the elafibranor group.

The 8% response rate in the placebo group (calculated as the mean response rate based on the Phase II FLINT study[35] [subanalysis including only patients with stage 2 and stage 3 fibrosis or stage 1 fibrosis with diabetes, obesity or ALT ≥ 60 {associated with fibrosis progression}; placebo response rate 6.5%] and the GFT505-212-7 placebo data [11% response rate for patients with any stage fibrosis {F1; F2; F3} and 7% response rate for patients with only stage 2 and 3 fibrosis]). The 16.5% response rate in the elafibranor group is based on the Phase II GFT505-212-7 elafibranor data (calculated as the mean response rate based on a 20% response rate for patients with any stage fibrosis ([F1; F2; F3] and 13% response rate for patients with only stage 2 and 3 fibrosis).

Based on these assumptions, a sample size of 1023 patients provides 90% power to show that elafibranor is superior to the placebo with respect to resolution of NASH without worsening of fibrosis.

9.7.2. Time to clinical event/death

The following assumptions were made for the sample size calculation for time to clinical event/death:

- 24 month enrollment (with an 18-month ramp up to as many as 200 patients per month)
- 72 month maximum follow-up
- α=0.04 two-sided
- Annual event rate of 7% for the placebo group
- Hazard ratio of 0.75 in favor of the elafibranor group
- 4% annual drop-out rate over 72 months
- Randomization ratio of 2:1 (elafibranor: placebo).

The 7% annual event rate in the placebo group is based on published literature on developing cirrhosis in patients with NASH and advanced fibrosis (F2-F3).[21,22,23,24,25] The rate of developing cirrhosis was estimated to be 7% (based on 8% per year in F3 patients and 6% per year in F2 patients). In a conservative approach, no additional event rate was added for other events than histological cirrhosis or cirrhosis decompensation events. An annual clinical event/death rate of 7% was thus defined for the composite of both these endpoints.

There is no long-term randomized clinical trial in a NASH population with moderate and severe liver fibrosis. In the 72-week FLINT trial, the total drop-out rate was 6.7%.[35] Therefore, we estimate an approximate annual drop-out rate of 4%. Based on these assumptions, 456 events are required to provide 80% power to show that elafibranor is superior to placebo with respect to time to clinical event/death. In order to obtain 456 events, at least 2022 patients will be required in the IIT.

9.8. SAFETY ANALYSIS

Safety data (exposure, AEs, clinical laboratory tests, vital signs, and ECGs) will summarized by treatment group using descriptive statistics. The main summaries of safety will be based on the SS. Additional safety analysis will be based on the FSS and the exploratory F1 cohort.

Adverse events will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA). An overall summary of AEs will be provided. The number and percentage of patients reporting AEs will also be presented by MedDRA System Organ Class and preferred term. The AEs will be summarized by worst severity and relationship to study drug. Serious AEs, and AEs leading to discontinuation will also be summarized. Narratives will be added for all SAE.

Clinical laboratory tests (hematology, chemistry, and urinalysis) recorded at each timepoint and change from baseline will be summarized by treatment group using descriptive statistics. Clinical laboratory values for each parameter will be assigned a classification according to whether the value is lower than, within, or higher than the reference range for that parameter. The values will then be summarized using shift tables to evaluate categorical changes from baseline to end of the 72 week treatment period with respect to reference ranges. The number and percentage of patients reporting markedly abnormal clinical laboratory values will also be summarized by treatment group.

Liver and kidney related laboratory tests including an assessment of DILI will also be summarized.

Vital signs recorded at each timepoint and change from baseline will be summarized by treatment group using descriptive statistics.

9.8.1. Surrogate endpoint analysis

The analysis of resolution of NASH without worsening of fibrosis will occur when 1023 F2 and F3 patients complete 72 weeks of treatment or discontinue early from the study. The null hypothesis will be tested at the two-sided 0.01 alpha level.

At this time, a snapshot of the database will be cleaned and locked for analysis and potential Subpart H or conditional approval submission. This analysis will be done by an unblinded team separate from the study team; the study team will not be unblinded until the final analysis at the end of follow-up.

The DSMB will also periodically review safety data from the study to ensure the well-being of study participants. These safety reviews will be based on reports generated by the SAC and may include select efficacy results so that the DSMB can assess the likely benefit-risk profile of elafibranor. These are not considered a formal interim analysis, and no type I error adjustments will be done for these reviews. Details will be in the DSMB Charter.

9.9. INTERIM ANALYSIS

An adaptive design interim analysis will be performed after 140 primary events (approx. 30% of the 456 required events) have been accrued. The interim analysis will be performed by an unblinded team separate from the study team. The Data Safety Monitory Board (DSMB) will review the interim analysis results and provide final recommendations regarding trial termination due to futility and adjustment of the target number of primary events. Details will be in the DSMB Charter and SAP.

10. DATA HANDLING AND RECORD KEEPING

10.1. CASE REPORT FORM AND SOURCE DOCUMENTS

A case report form (CRF) is required and should be completed for each screened patient. The completed eCRFs are the sole property of the Sponsor and should not be made available in any form to third parties, except for authorized Sponsor's representatives or appropriate regulatory authorities, without written permission from the Sponsor.

The Investigator will ensure that all data are entered promptly, legibly, completely, accurately and conform to source documents, in accordance with specific instructions accompanying the eCRFs designed specifically for this study. The CRF being used for this study is an electronic CRF that has been fully certified as being compliant with the FDA regulations at 21 Code of Federal Regulations (CFR) Part 11.

All study required patient data generated during the study will be recorded in the eCRF, with the exception of SAE forms and SF-36 which will be collected via ePRO (which is then transferred to the electronic data capture). Patients will not be identified by name in the eCRF or on any study documents to be collected by the Sponsor (or designee), but will be identified by a patient number.

The Investigator will review and approve each completed eCRF; the Investigator's validation serving as attestation of the Investigator's responsibility for ensuring that all clinical and laboratory data entered in the eCRF are complete, accurate, and authentic.

Should a correction be made, the corrected information will be recorded in the eCRF by the authorized person and explained (if necessary). All corrected data will be tracked through an audit trail.

It is the Investigator's obligation to ensure documentation of all relevant data in the patient's medical file (medical history, concomitant diseases, patient identification number, date of informed consent, visit dates, administration of study medication, AEs [start and stop dates] and all concomitant medications [start and stop dates]). All data recorded in the eCRF will be documented by source data.

10.2. RETENTION OF RECORDS

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified.

The Investigator will be provided with a study file, which should be used to file the Investigator Brochure, protocol/amendments, drug accountability records, sample informed consent, staff curriculum vitae, correspondence with the IRB/IEC, Sponsor, and other study-related documents.

To enable evaluations and/or audits from regulatory authorities or the Sponsor, the Investigator agrees to keep records, including the identity of all participating patients, all original signed ICFs, copies of all eCRFs, source documents, and detailed records of treatment disposition.

The Investigator must retain the study documentation until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. However these documents should be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the Sponsor. All hospital records will be archived according to local regulation.

The Sponsor should be notified if the Investigator relocates, retires, or for any reason withdraws from the trial. The trial records must be transferred to an acceptable designee, such as another Investigator, another institution, or to the Sponsor.

11. QUALITY CONTROL AND QUALITY ASSURANCE

11.1. QUALITY CONTROL & MONITORING PROCEDURES

It is the responsibility of the Investigator to ensure that the study is conducted in accordance with the protocol, Good Clinical Practice (ICH topic E6), applicable regulatory requirements, and the current Declaration of Helsinki (APPENDIX I: World Medical Association Declaration of Helsinki) and that valid data are entered into the eCRFs.

To achieve this objective, the Study Monitor's duties are to aid the Investigator and, at the same time, the Sponsor in the maintenance of complete, legible, well-organized, and easily retrievable data.

Before enrolling any patients in this study, the Study Monitor will review the protocol, the brochure for clinical investigators, the eCRFs and instructions for their completion and return, the procedure for obtaining informed consent, and the procedure for reporting AEs and SAEs with the Investigator. In addition, the Study Monitor will explain the Investigator's reporting responsibilities and all applicable regulations concerning the clinical evaluation of the study drug.

The Investigator will permit the representatives of Sponsor to monitor the study as frequently as the Sponsor deems is necessary to determine that data recording and protocol adherence are satisfactory. A Study Monitor from [redacted] Late Stage Development Services will be responsible for monitoring this clinical trial. To this end, the Study Monitor will visit the study site at suitable intervals and be in frequent contact through verbal and written communication. The eCRFs and related source documents, as well as drug accountability will be reviewed in detail by the monitor at each visit, in accordance with relevant SOPs and Good Clinical Practice (GCP; ICH topic E6) regulations. This includes results of tests performed as a requirement for participation in this study and any other medical records required to confirm information contained in the eCRFs, such as past medical history and secondary diagnoses.

A risk based monitoring strategy will be used for this study. Study monitoring strategy design will be based on overall study risk assessment. Individual site monitoring strategy design will be based on individual site risk assessment. On site monitoring will focus on source document verification of mandatory and critical data and source document review of critical processes, and will be supported by formal remote site monitoring activities. Centralized monitoring activities will review study data to assess changes in individual site risk and to identify emerging trends, risks and issues across sites, countries, regions, and the global study. Further details can be found in the Monitoring Plan.

It is essential that the Study Monitor has access to all documents (related to the study and the individual participants) at any time these are requested. In turn, the Study Monitor will adhere to all requirements for patient confidentiality as outlined in the ICF. The Investigator and Investigator's staff will be expected to cooperate with the Study Monitor, to be available during a portion of the Monitoring Visit to answer questions, and to provide any missing information.

All monitoring activities will be reported and archived in the Trial Master File.

11.2. ETHICAL PRINCIPLES

This protocol complies with the principles laid down by the 18th World Medical Assembly (Helsinki, 1964) and all applicable amendments laid down by the World Medical Assemblies (APPENDIX I: World Medical Association Declaration of Helsinki), and the GCP guideline.

This trial also complies with applicable local regulatory requirements and laws of each country in which the study is performed, as well as any applicable guidelines.

11.3. QUALITY ASSURANCE

For the purpose of ensuring compliance with the protocol, GCP and applicable regulatory requirements, the Investigator should permit auditing by the Sponsor and/or designee and inspection by applicable regulatory authorities. The Investigator agrees to allow the auditors/inspectors to have direct access to his/her study records for review, being understood that these personnel will adhere to all requirements for patient confidentiality, and as such will not disclose any personal identity or personal medical information.

As soon as the Investigator is notified of a future inspection by the Authorities, he/she will inform the Sponsor and authorize the Sponsor to participate at this inspection.

The confidentiality of the data verified and the anonymity of the patients should be respected during these inspections.

Clinical data associates from the Sponsor's representative will review the data for completeness and logical consistency. Additionally, the clinical data associates will use automated validation programs to help identify missing data, selected protocol violations, out of range data, and other data inconsistencies. Requests for data clarification or correction will be electronically provided to the investigative site for resolution. Clinical data associates will assure that corrections have been applied properly.

12. ETHICS AND REGULATORY

12.1. INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE

The GCP guidelines and the US CFR Title 21 Section 56 (21 CFR 56) require that approval must be obtained from an Independent Ethics Committee (IRB/IEC) prior to participation of human patients in research studies. Prior to the study onset, the protocol, ICF, advertisements to be used for patient recruitment, and any other written information regarding this study to be provided to the patient or the patient's legally acceptable representative must be approved by the IRB/IEC. The Sponsor will supply relevant material for the Investigator to submit to the IRB/IEC for the protocol's review and approval. Verification of the IRB's unconditional approval of the protocol and the written ICF statement will be transmitted to the Investigator. Documentation of the relevant IRB/IEC approval and of the IRB/IEC compliance with GCP guideline will be maintained by the site and will be available for review by the Sponsor or its designee or by the authorized members of regulatory agencies.

The Applicant must supply the Sponsor with written documentation of the initial favorable opinion of the clinical research before the start of the trial.

The study will not commence until favorable opinion has been obtained from the appropriate IRB/IEC.

If any alterations, other than changes of administrative nature only, are made to the study protocol, a formal protocol amendment will be issued. The IRB/IEC will be informed by the Investigator of subsequent protocol amendments and of SUSARs. Approval for protocol amendments will be transmitted in writing to the Investigator.

The amendment will not be implemented until IRB/IEC approval, except in cases where immediate implementation is necessary to eliminate or prevent imminent hazard to the patients. A protocol change intended to eliminate an apparent immediate hazard must be documented in an amendment, reported to the IRC/IEC within 5 working days, and submitted to the appropriate regulatory agencies in the required time frame.

If requested, the Investigator will permit audits by the IRB/IEC and regulatory inspections by providing direct access to source data/documents.

The Investigator will provide the IRB/IEC with progress reports at appropriate intervals (not to exceed 1 year) and a Study Progress Report following the completion, termination, or discontinuation of the Investigator's participation in the study.

12.2. COMPETENT AUTHORITY

In the same way as for IRB/IEC (see Section 12.1), when required by national regulation, approval from Competent Authorities (CA) should be granted before the beginning of the study. If applicable, Amendments will also be submitted to CA for approval.

12.3. PATIENT INFORMATION AND CONSENT

Written informed consent for the study will be obtained from each patient before protocol-specific procedures are carried out. The ICF used by the Investigator for obtaining the patient's Informed Consent must be reviewed and approved by the Sponsor prior to submission to the appropriate ethics committee (IRB/IEC). The ICF will be approved (along with the protocol) by the IRB/IEC.

In the case of any exploratory substudies, specific study documents will be prepared and IRB/IEC and authority approvals shall be obtained when applicable.

The Investigator or a person designated by the Investigator (according to applicable regulatory requirements), will explain the nature of the study and the action of the test product. The patients will be informed that participation is voluntary and that they can withdraw from the study at any time. In accordance with 21 CFR 50, the informed consent process shall be documented by the use of a written ICF approved by the designated IRB/IEC and will be signed and personally dated by the patient or by the patient's legally acceptable representative and by the person who conducted the informed consent discussion prior to protocol-specific procedures being performed. A separate consent form will be obtained for optional genetic and biomarker samples to be stored in the blood bank.

The Investigator must maintain the original, dated and signed ICF. A copy of the signed ICF must be given to the patient.

12.4. PATIENT CONFIDENTIALITY

The Sponsor will affirm and uphold the principle of the patient's right to protection against the invasion of privacy. Throughout this study and any subsequent data analyses, all data will be identified only by protocol number and patient number.

All unpublished information that the Sponsor gives to the Investigator shall be kept confidential and shall not be published or disclosed to a third party without the prior written consent of the Sponsor.

When the Sponsor generates reports for presentations to regulatory agencies, one or more of the Investigators who has/have contributed significantly to the study will be asked to endorse the final report. The endorsement is required by some regulatory agencies.

The Investigator shall not make a patent application based on the results of this study and shall not assist any third party in making such an application without the written authorization of the Sponsor unless otherwise specified in the CSA.

12.5. DEFINITION OF THE END OF THE RESEARCH

End of the research corresponds to the end of participation (end of study EOT Visit) of the last patient participating in the research.

13. FINANCING AND INSURANCE

13.1. FINANCIAL ISSUES

Financial contracts will be signed between the Sponsor and the Investigator/Institution before initiation of the study.

13.2. INSURANCE AND PATIENT INJURY

The patients taking part in the trial will be covered by the insurance taken by the Sponsor for this trial, if they were to suffer any prejudice as a result of taking part in the trial.

In general, if a patient is injured as a direct result of the study drug, the Sponsor will pay for reasonable and necessary medical treatment for the injury, to the extent the expenses are not covered by the patient's medical insurance, a government program, or other responsible third party. If laws or regulations of the locality in which the trial is taking place require additional payment of expenses, the Sponsor shall comply with such law or regulation.

The Sponsor certifies to have taken out an insurance policy to cover the financial consequences of its civil liability and that of everyone involved in the research, and notably that of the Investigators and their colleagues with regard to any accidents or damage concerning the administration of the drug or paraclinical examinations directly linked to the performance of the trial.

14. STUDY RESULTS AND PUBLICATION POLICY

14.1. STUDY REPORT

The final report will be written in ENGLISH upon completion of study and statistical analysis according to ICH E3 guideline. The report or part of it must be submitted to relevant authorities if applicable.

[redacted] will prepare an integrated clinical and safety report. Prior to issuing the final CSR, [redacted] will prepare a draft report for approval by the Sponsor. The report will be in accordance with the ICH E3 Guideline for Industry: Structure and Content of CSRs. The draft report will be submitted for Quality Assurance audit, the findings of which will be incorporated into the final version.

An electronic copy of the final CSR will be made available to the Sponsor. The study report will be provided in PDF and MS Word formats unless agreed otherwise by [redacted] Reports requiring specialized Sponsor formats/alternative computer software packages may be possible on request from the Sponsor but may involve extra time and cost. Electronic datasets will also be provided to the Sponsor on issuance of the final report.

After review by the Sponsor, a final CSR will be submitted to the Sponsor which incorporates the Sponsor's comments.

14.2. CONFIDENTIALITY AND OWNERSHIP OF DATA, USE OF THE STUDY RESULTS AND PUBLICATION

All materials, information (oral or written), and unpublished documentation provided to the Investigators (or any company/institution acting on their behalf), including this protocol, the patient CRFs, and the Investigator's Brochure, are the exclusive property of the Sponsor and may not be published, given, or disclosed, either in part or in whole, by the Investigator or by any person under his/her authority to any third party without the prior express consent of the Sponsor.

However, the submission of this protocol and other necessary documentation to the ethics committee (IRB/IEC) and the Competent Authority is expressly permitted, their members having the same obligation of confidentiality.

The Investigator shall consider all information, results, discoveries, records (accumulated, acquired, or deduced) in the course of the study, other than that information to be disclosed by law, as confidential and shall not disclose any such results, discoveries, or records to any third party without the Sponsor's prior written consent.

The Sponsor retains exclusive ownership of all data, results, reports, findings, discoveries, and any other information collected during this study. Therefore, the Sponsor reserves the right to use the data from the present study, either in the form of Case Report Forms (or copies of these), or in the form of a report, with

or without comments and with or without analysis, in order to submit them to the Health Authorities of any country.

When the Sponsor generates reports for presentations to regulatory agencies, one or more of the Investigators who has/have contributed significantly to the study will be asked to endorse the final report. The endorsement is required by some regulatory agencies.

Furthermore, in the event that the study generates patentable results, the Investigator (or entity acting on his/her behalf according to local requirements) shall refrain from filing patent application(s) on such results, which will be filed by the Sponsor or its designees in its own name and at its expense.

Clinical study will be registered on the open access website http://www.clinicaltrials.gov before the screening of the first patient in the study.

It is the policy of the Sponsor to encourage the presentation and/or publication of the results of their studies, using only clean, checked, and validated data in order to ensure the accuracy of the results.

The publication of study results will be agreed between the Sponsor and the Investigators.

At least 45 days in advance of proposed submission, the Investigator should forward a copy of the manuscript or abstract for review by the Sponsor, and, if necessary, delay publication or communication for a limited time in order to protect the confidentiality or proprietary nature of any information contained therein. The Sponsor may also request that the Sponsor's name and/or names of one or several of its employees appear or not appear in such publication.

15. REFERENCES LIST

1. Day CP, James OF. Steatohepatitis: a tale of two "hits"? *Gastroenterology*. 1998;114:842-845.
2. Jou J, Choi SS, Diehl AM. Mechanisms of disease progression in nonalcoholic fatty liver disease. *Semin Liver Dis*. 2008;28: 370-379.
3. Edmison J, McCullough AJ. Pathogenesis of nonalcoholic steatohepatitis: human data. *Clin Liver Dis*. 2007;11:75-104.
4. Browning JD, Horton JD. Molecular mediators of hepatic steatosis and liver injury. *J Clin Invest*. 2004;114:147-152.
5. Ikejima K, Honda H, Yoshikawa M, et al. Leptin augments inflammatory and profibrogenic responses in the murine liver induced by hepatotoxic chemicals. *Hepatology*. 2001;34: 288-297.
6. Poniachik J, Santibanez C, Haim D, et al. Enhancement in liver nuclear factor-kb (NF-KB) and activator protein 1 (AP-1) DNA binding in obese patients with nonalcoholic fatty liver disease. The 43rd Annual Meeting of the European Association for the Study of the Liver. Milan, Italy, 2008.
7. Yamauchi T, Kamon J, Minokoshi Y, et al. Adiponectin stimulates glucose utilization and fatty-acid oxidation by activating AMP-activated protein kinase. *Nat Med*. 2002;8(11):1288-95. Epub 2002 Oct 7.
8. Targher G, Bertolini L, Rodella S, et al. Associations between plasma adiponectin concentrations and liver histology in patients with nonalcoholic fatty liver disease. *Clin Endocrinol (Oxf).* 2006;64:679-683.
9. Xu H, Barnes G, Yang Q, et al. Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance. *J Clin Invest*. 2003;112(12):1821-1830.
10. Pessayre D, Fromenty B, Mansouri A. Mitochondrial injury in steatohepatitis. *Eur J Gastroenterol Hepatol*. 2004;16:1095-1105.
11. Crespo J, Cayon A, Fernandez-Gil P, et al. Gene expression of tumor necrosis factor alpha and TNF-receptors, p55 and p75, in nonalcoholic steatohepatitis patients. *Hepatology*. 2001;34:1158–1163.
12. Hotamisligil GS, Arner P, Caro JF, et al. Increased adipose tissue expression of tumor necrosis factor-alpha in human obesity and insulin resistance. *J Clin Invest.* 1995;95:2409-2415.
13. Ramalho RM, Cortez-Pinto H, Castro RE, et al. Apoptosis and Bcl-2 expression in the livers of patients with steatohepatitis*. Eur J Gastroenterol Hepatol*. 2006;18:21-29.
14. Laurin J, Lindor KD, Crippin JS, et al. Ursodeoxycholic acid or clofibrate in the treatment of nonalcohol-induced steatohepatitis: a pilot study. *Hepatology*. 1996;23(6):1464-1467.
15. Shan W, Nicol CJ, Bility MT, et al. Peroxisome proliferator-activated receptor-beta/delta protects against chemically induced liver toxicity in mice, *Hepatology*. 2008;47(1):225-235.
16. Risérus U, Sprecher D, Johnson T, et al. Activation of peroxisome proliferator-activated receptor (PPAR) delta promotes reversal of multiple metabolic abnormalities, reduces oxidative

stress, and increases fatty acid oxidation in moderately obese men. *Diabetes*. 2008;57(2):332-339. Epub 2007 Nov 16.

17. Kang K, Reilly SM, Karabacak V, et al. Adipocyte-derived TH2 cytokines and myeloid PPAR delta regultate macrophage polarization and insulin sensitivity. *Cell Metab.* 2008;7:485-495.
18. Odegaard JI, Ricardo-Gonzalex RR, Red Eagle A et al. Alternative M2 activation of Kupffer cells by PPARδ ameliorates obesity induced insulin resistance. *Cell Metab*. 2008;7:496-507.
19. Cattley RC, Deluca j, Elcombe C, et al. Do peroxisome proliferating compounds pose a hepatocarcinogenic hazard to humans? *Regul Toxicol Pharmacol*. 2008;27(1 Pt 1):47-60.
20. Musso G, Gambino R, Cassader M, Pagano G . Meta-analysis: natural history of nonalcoholic fatty liver disease (NAFLD) and diagnostic accuracy of non-invasive tests for liver disease severity. *Ann Med*. 2011;43(8):617-649.
21. Ekstedt M, Franzen LE, Mathiesen UL, et al. Long-term follow-up of patients with NAFLD and elevated liver enzymes. *Hepatology.* 2006;44(4):865-873.
22. Angulo P, Kleiner DE, Dam-Larsen S, et al. Liver Fibrosis, but No Other Histologic Features, Is Associated With Long-term Outcomes of Patients With Nonalcoholic Fatty Liver Disease. *Gastroenterology.* 2015;149(2):389-397 e310.
23. Argo CK, Northup PG, Al-Osaimi AM, Caldwell SH . Systematic review of risk factors for fibrosis progression in nonalcoholic steatohepatitis. *J Hepatol*. 2009;51(2):371-379.
24. Pagadala MR, McCullough AJ. The relevance of liver histology to predicting clinically meaningful outcomes in nonalcoholic steatohepatitis. *Clin Liver Dis* 2012;16(3):487-504.
25. Singh S, Allen AM, Wang Z, Prokop LJ, Murad MH, Loomba R. Fibrosis progression in nonalcoholic fatty liver vs nonalcoholic steatohepatitis: a systematic review and meta-analysis of paired-biopsy studies. *Clin Gastroenterol Hepatol.* 2015;13(4):643-654.
26. Hashimoto E, Tokushige K. Prevalence, gender, ethnic variations, and progression of NASH. *J Gastroenterol.* 2011;46(supplement 1):63-69.
27. Younossi ZM, Stepanova M, Rafiq N, et al. Pathologic criteria for nonalcoholic steatohepatitis: interprotocol agreement and ability to predict liver-related mortality. *Hepatology.* 2011;53(6):1874-1882.
28. Ratziu V, de Ledinghen V, Oberti F, et al. A randomized controlled trial of high-dose ursodesoxycholic acid for nonalcoholic steatohepatitis. *J Hepatol.* 2011;54(5):1011-1019.
29. Sanyal AJ, Brunt EM, Kleiner DE, et al. Endpoints and clinical trial design for nonalcoholic steatohepatitis. *Hepatology*. 2011;54:344-353.
30. Sanyal AJ, Friedman SL, McCullough AJ, et al. Challenges and opportunities in drug and biomarker development for nonalcoholic steatohepatitis: findings and recommendations. *Hepatology.* 2015;61(4):1392-1405.
31. McPherson S, Hardy T, Henderson E, et al. Evidence of NAFLD progression from steatosis to fibrosing-steatohepatitis using paired biopsies: implications for prognosis and clinical management. *J Hepatol*. 2015;62(5):1148-1155.

32. Dunn W, Xu R, Wingard DL, et al. Suspected nonalcoholic fatty liver disease and mortality risk in a population-based cohort study. *Am J Gastroenterol.* 2008;103(9):2263-2271.
33. Rafiq N, Bai C, Fang Y, et al. Long-term follow-up of patients with nonalcoholic fatty liver. *Clin Gastroenterol Hepatol.* 2009;7(2):234-328.
34. Clinical Trial Facilitation Group (2014). Recommendations related to contraception and pregnancy testing in clinical trials. Available at: http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf
35. Neuschwander-Tetri BA, Loomba R, Sanyal AJ, et al. Farnesoid X nuclear receptor ligand obeticholic acid for non-cirrhotic, nonalcoholic steatohepatitis (FLINT): a multicentre, randomised, placebo-controlled trial. *Lancet*. 2015;385(9972):956-965.
36. Saville RS and Koch G. Estimating Covariate-Adjusted Log Hazard Ratios in Randomized Clinical Trials Using Cox Proportional Hazards Models and Nonparametric Randomization Based Analysis of Covariance. Journal of Biopharmaceutical Statistics. 2013 23: 477-490.
37. Zink RC and Koch G. NParCov3: A SAS/IML Macro for Nonparametric Randomization-Base Analysis of Covariance. Journal of Statistical Software. 2012 July 50:3.

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Appendices

APPENDIX I: WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

"The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by

individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

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19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and

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standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

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27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain

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for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made

publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

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APPENDIX II: ADEQUATE DIET AND LIFESTYLE RECOMMENDATIONS

Essential Components of Therapeutic Lifestyle Changes (TLC)

Component	Recommendation
LDL-raising nutrients	
Saturated fats*	Less than 7% of total calories
Dietary cholesterol	Less than 200 mg/day
Therapeutic options for LDL lowering	
Plant stanols/sterols	2 grams per day
Increased viscous (soluble) fiber	10–25 grams per day
Total calories (energy)	Adjust total caloric intake to maintain desirable body weight/prevent weight gain
Physical activity	Include enough moderate exercise to expend at least 200 kcal per day

* *Trans* fatty acids are another LDL-raising fat that should be kept at a low intake.

Macronutrient Recommendations for the TLC Diet

Component	Recommendation
Polyunsaturated fat	Up to 10% of total calories
Monounsaturated fat	Up to 20% of total calories
Total fat	25–35% of total calories*
Carbohydrate†	50–60% of total calories*
Dietary fiber	20–30 grams per day
Protein	Approximately 15% of total calories

* ATP III allows an increase of total fat to 35 percent of total calories and a reduction in carbohydrate to 50 percent for persons with the metabolic syndrome. Any increase in fat intake should be in the form of either polyunsaturated or monounsaturated fat.
† Carbohydrate should derive predominantly from foods rich in complex carbohydrates including grains—especially whole grains—fruits, and vegetables.

APPENDIX III: PERMITTED/NON-PERMITTED MEDICATION

Table I: NON-PERMITTED MEDICATION AND CONDITION

Medications	**When**
Same pharmacological class (PPAR agonists)	
Thiazoledinediones (glitazones [pioglitazone and rosiglitazone])	From 6 months prior to diagnostic liver biopsy* up to end of study treatment (EOT) Visit
Fibrates	From 2 months prior to Randomization up to EOT Visit
Medication that may induce steatosis/steatohepatitis	
Corticosteroids (parenteral & oral chronic administration)	From 30 days prior to first Screening Visit up to EOT Visit
Amiodarone	
Tamoxifen	
Methotrexate	
Medication that may interact with absorption, metabolism, etc	
Indomethacin	From Randomization up to EOT Visit

* Given the potential effect on diagnostic liver biopsy of patients previously treated by glitazones

Table II: PERMITTED MEDICATION AND CONDITION

Medications	When
Antidiabetic therapy	
GLP-1 agonist	Dose stability required in the 6 months prior to the diagnostic liver biopsy No qualitative change (i.e., no initiation of a new drug) from at least 6 months prior to the diagnostic liver biopsy up to 72-week of treatment (V7). Dose changes after randomization should be avoided
All other ATD therapy (insulin, sulfonylureas, metformin, gliptins)	No qualitative change (i.e., no initiation of a new drug) from at least 6 months prior to the diagnostic liver biopsy and up to Randomization(Dose changes are allowed). Dose changes after randomization are allowed.
SGLT2-inhibitors	No qualitative change (i.e., no implementation of a new drug)from at least 6 months prior to the diagnostic liver biopsy up to 72-weeks of treatment (V7). Dose changes after randomization should be avoided.
Lipid lowering therapy	
Statins	Dose stability required from at least 2 months prior to Screening . Dose changes are allowed after Randomization if judged necessary by the physician
Ezetimibe	
Other nonfibrate lipid lowering therapies	
Others	
Vitamin E >400 IU/day	Dose stability required from at least 6 months prior to the diagnostic liver biopsy. Dose changes should be avoided up to EOT
PUFAs >2 g/day	
Ursodeoxycholic acid	

Abbreviations: ATD = autoimmune thyroid disease; EOT = end of study treatment; GLP-1 =glucagon-like peptide 1; PUFA = polyunsaturated fatty acids; SGLT2 = sodium/glucose cotransporter 2.

APPENDIX IV: ALCOHOL COMPARISON TABLE

Alcohol type	Alcohol by volume (ABV)	Volume		Amount of alcohol	
		Fluid ounce	mL	Units [2]	grams
Beer	3.5%	12	350	0.7	9.8
Beer	5%	12	350	1	14
Cider	7%	12	350	1.4	19.6
Distilled spirits or liquor [1]	40%	1.5	45	1	14
Wine	12%	5	150	1	14

1. e.g., gin, rum, vodka, whiskey.
2. Units calculated using the cleave Books calculator for units of drink, using the US definition of 1 unit of alcohol as 17.7 mL (14.0 g) of pure alcohol (http://www.cleavebooks.co.uk/scol/ccalcoh3.htm).

APPENDIX V: PRODUCT CARTON AND WALLET LABELING

	Carton	Wallet
Protocol number	X	X
Sponsor details	X	X
Site number	X	-
Subject ID	X	X
Kit number	X	X
Visit number	X	-
Lot number	X	X
Expiry date	X	X
Contents	X	X
Route of administration	X	X
Administration instructions	X	X
"For Clinical Trial Use only."	X	X
"Keep out of reach of Children."	X	X
Storage details	X	X
Instructions for product and package return at next visit	X	X

GENFIT
TOWARDS BETTER MEDICINE

CLINICAL PROTOCOL – PHASE 3

Protocol N° GFT505-315-1

EudraCT N°2015-005385-38

IND number: 115028

Amendment 2: Final 3.0 – Release date 03 April 2017

Supersedes previous Version 2.0 - Release date: 06 January 2017

A Multicenter, Randomized, Double-Blind, Placebo-Controlled Phase III Study to Evaluate the Efficacy and Safety of Elafibranor in Patients with Nonalcoholic Steatohepatitis (NASH) and fibrosis

International Coordinating Investigator Committee	[redacted]	[redacted]
Sponsor	**GENFIT**	Parc Eurasanté 885, Avenue Eugène Avinée 59120 LOOS, France
Represented by:	[redacted]	[redacted]

CLINICAL STUDY PROTOCOL SIGNATURE PAGE

Protocol N°: **GFT505-315-1 / EudraCT N° 2015-005385-38/ IND n°115028**

Version number: **3.0**

Release date: **03 April 2017**

TITLE: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Phase III Study to Evaluate the Efficacy and Safety of Elafibranor in Patients with Nonalcoholic Steatohepatitis (NASH) and fibrosis.

In signing below, I give agreement to the protocol.
International Coordinators:

[redacted]

Signature

[redacted]

Date (dd-mmm-yyyy)

CLINICAL STUDY PROTOCOL SIGNATURE PAGE

Protocol N°: **GFT505-315-1 / EudraCT N° 2015-005385-38/ IND n°115028**

Version number: **3.0**

Release date: **03 April 2017**

TITLE: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Phase III Study to Evaluate the Efficacy and Safety of Elafibranor in Patients with Nonalcoholic Steatohepatitis (NASH) and fibrosis.

In signing below, I give agreement to the protocol.

[redacted]

[redacted]

Date (dd-mmm-yyyy)

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In signing below, I give agreement to the protocol.

[redacted]

Signature

[redacted]

Date (dd-mmm-yyyy)

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In signing below, I give agreement to the protocol.

On behalf of (the Sponsor): GENFIT
Parc Eurasanté
885, Avenue Eugène Avinée
59120 LOOS – France

Name: [redacted]

[redacted] _____ [redacted]

Signature *Date (dd-mmm-yyyy)*

CLINICAL STUDY PROTOCOL

INVESTIGATOR SIGNATURE PAGE

PROTOCOL TITLE: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Phase III Study to Evaluate the Efficacy and Safety of Elafibranor in Patients with Nonalcoholic Steatohepatitis (NASH) and fibrosis.

PROTOCOL NUMBER: GFT505-315-1

EudraCT Number: 2015-005385-38

IND Number: 115028

CLINICAL PHASE: III

VERSION: 3.0

DATE: April 03, 2017

SPONSOR: GENFIT,
Parc Eurasanté,
885 Avenue Eugène Avinée,
59120 LOOS - France

In signing below, I confirm having read the protocol, and give agreement to the protocol.

INVESTIGATOR NAME: _____

INSTITUTION NAME: _____

INSTITUTION ADDRESS: _____

_____

SIGNATURE: _____

DATE: _____ /_____ /_____

Day Month Year

STUDY CONTACTS

Protocol N°: **GFT505-315-1/ EudraCT N° 2015-005385-38/ IND n° 115028**

International Coordinating Investigator Committee	[redacted]	[redacted]
Sponsor	GENFIT	Parc Eurasanté 885, Avenue Eugène Avinée 59120 LOOS - France
CRO for monitoring, data management & statistics	[redacted]	[redacted]
Pharmacovigilance	[redacted]	[redacted]

IXRS	[redacted]
Study drug supplier	[redacted]
Central laboratory	[redacted]
Central pathology laboratory	[redacted]
ePRO	[redacted]

AMENDMENT 2: 2017

Amendment 2 is a non substantial change to clarify the collection of 2 baseline values of liver enzymes before study treatment initiation. This remains in line with the FDA request to obtain 2 baseline values of liver transaminase, total bilirubin, and INR at least 8 weeks apart, in order to be able to have 2 baseline values in case of DILI adjudication. Added text is **bolded**; deleted text is ~~struck through~~.

Summary of changes to the protocol:

Section	**New Text**
Table 1: STUDY GENERAL ASSESSMENT SCHEDULE	Table 1 updated with changes related to the screening period [4] **The visits to be performed during the screening period should be scheduled according to the following requirements:** - **If there are historical lab values for AST, ALT, total bilirubin and INR that are within 8 weeks to 6 months of the planned Randomization visit (V1) these results can be used as the first baseline values in case of DILI adjudication. If there are no historical lab values that meet this requirement, then SV1 and V1 must be scheduled at least 8 weeks apart.** - ~~This~~ The visit **SV2** only occurs if no historical biopsy within 6 months before the Screening Visit is available. A

Section	**New Text**
	screening liver biopsy and slides shipment to the central pathologist must be performed at least 4 weeks before Randomization,~~(~~in order to obtain the results in time~~)~~. **However, in some exceptional cases, the central reading process can be expedited allowing a shorter time between SV1 or SV2 and V1.** Coagulation (platelet count and PT [INR]) should be checked locally prior to this liver biopsy (according to local medical standards in each hospital). - **Randomization visit can be scheduled as soon as all the results are available to confirm the eligibility of the patients**
Table 2: STUDY BIOLOGICAL ASSESSMENT SCHEDULE	Table 2 updated with changes related to the screening period 6. **If no historical values of AST, ALT, total bilirubin and INR meeting the requirements of within 8 weeks to 6 months of planned randomization visit (V1) are available, then SV1 and V1 must be scheduled at least 8 weeks apart in order to have 2 consecutive values for DILI adjudication. In any case, the visits should be scheduled in order to obtain the needed results prior to the randomization.**
Figure 1: STUDY DURATION AND VISIT SCHEDULE	Figure updated with changes related to the screening period

Section	**New Text**
Figure 2: PREGNANCY	Figure updated with changes related to the screening period

Section	**New Text**
TESTING SCHEDULE FOR WOMEN OF CHILDBEARING POTENTIAL	
Section 3.6.1	3.6 - SCREENING PERIOD **(WEEK -12 TO WEEK -1)** 3.6.1 - Screening visits SV1 ~~(Week -12 to Week -8)~~ and SV2 ~~(Week -12 to Week -4):~~

Section	**New Text**
	The following screening procedures will be performed for all potential patients at SV1 conducted ~~between~~ **during the screening period and prior to randomization** ~~Week -12 and Week -8 prior to Randomization~~: • Signature of informed consent witnessed by the Investigator or designated person. **Note**: The signature of the informed consent may also be performed before SV1. • Patient number allocation via IXRS. • Check medical history/demographics. • Check inclusion/exclusion criteria (described in Section 4). • Physical examination (described in Section 6.2.1). • Adequate diet recommendations (described in Section 5.1.1 and APPENDIX II: Adequate diet and lifestyle recommendations), alcohol restrictions (described in Section 5.1.2), and tobacco habits. • Record vital signs (described in Section 6.2.3). • Record height, weight, and waist circumference. • Check concomitant/prior medication (within 6 months prior to Screening) (described in Section 7.12 and APPENDIX III: Permitted/non-permitted medication) • Check if a liver biopsy with confirmed NASH and fibrosis is available, and, if so send sample for central confirmation of NASH diagnosis (described in Section 6.1.1.2). This historical diagnostic biopsy should be obtained within 6 months prior to the Screening Visit. • Check AEs from time of Informed Consent Form (ICF) signature (described in Section 6 and Section 8). The Screening biological assessment (SB1 will be scheduled at SV1). If no diagnostic liver biopsy (within 6 months of SV1) is available, it **is recommended to schedule** an additional SV2 visit ~~will be booked~~ at least Week -4 ~~(period between Screening and Week -4)~~ prior to the planned Randomization V1, **in order to obtain the results in time**. The following biological assessments (detailed in Table 2) will be performed at SB1: ☐Blood samples (described in Table 2). ☐Whole blood, plasma & serum bank samples (only if additional genetic and biomarker ICF signed).

Section	New Text
	☐Urinalysis dipstick. ☐Urinary pregnancy test (for women of childbearing potential only [WOCBP]). **If no historical values of AST, ALT, total bilirubin and INR meeting the requirements of within 8 weeks to 6 months of randomization visit are available, then SV1 and V1 must be scheduled at least 8 weeks apart in order to have 2 consecutive values for DILI adjudication.** ~~Visits SV1 and V1 should be scheduled at least 8 weeks apart in order to have 2 consecutive baseline values of AST, ALT, total bilirubin, and INR for DILI adjudication (using SV1 and V1 kits).~~
Section 3.6.2	3.6.2- Screening Visit SV2 (liver biopsy if required, Week -12 to **recommended** Week -4): If no diagnostic liver biopsy within 6 months of SV1 is available, **it is recommended to schedule** an additional SV2 visit ~~will be booked by~~ at least Week -4 for a liver biopsy to be performed (described in Section 6.1.1.1). Blood samples for coagulation (detailed in Table 2) will be taken and tested at a local laboratory prior to the liver biopsy. Liver biopsy samples will be sent for central confirmation of NASH diagnosis (described in Section 6.1.1.2).
Section 6.3.2	6.3.2 -Liver function monitoring All liver decompensation events included in the composite efficacy endpoint (Section 1.9.2) will be adjudicated by the Clinical Events Committee (CEC; see Section 6.5), as well as all DILI events (see Section 6.5). **For DILI adjudication, assessment may be performed using as baseline either historical AST, ALT, total bilirubin, and INR results meeting the requirements of within 8 weeks to 6 months of planned randomization visit (V1), or, using lab results from SV1 and V1 that are at least 8 weeks apart.** ~~For DILI adjudication, assessment may be performed using as baseline value the average obtained from measurements at the SV1 and V1 visits (described in the CEC Charter).~~ In all cases, whether baseline AT values are normal or elevated, an increase of AT >10 x ULN will lead to permanent discontinuation of the patient from study drug, and scheduling of EOT visit (Section 3.9).

CLINICAL TRIAL SYNOPSIS

Sponsor:	Study Drug:	Protocol Number:
GENFIT	Elafibranor (GFT505): Propanoic acid, 2-[2,6-dimethyl-4-[3-[4-(methylthio)phenyl]-3-oxo-1(E)-propenyl] phenoxy]-2-methylpropanoic acid	GFT505-315-1

Title of the study:
A Multicenter, Randomized, Double-Blind, Placebo-Controlled Phase III Study to Evaluate the Efficacy and Safety of Elafibranor in Patients with Nonalcoholic Steatohepatitis (NASH) and fibrosis

Phase:
Phase III
Indication:
NASH

Study design and dose levels:
Randomized, double-blind, parallel groups (placebo or elafibranor [GFT505]) placebo-controlled study, evaluating the efficacy and safety of elafibranor 120 mg QD versus placebo in an adult NASH population with fibrosis. The first double-blind 72-week treatment period will assess the efficacy and safety of elafibranor on the resolution of NASH without worsening of fibrosis at the surrogate endpoint efficacy analysis, followed by a Long-term Treatment Period (LTTP) to assess efficacy on progression to cirrhosis, all-cause mortality, and liver-related clinical outcomes as measured by the onset of any of the listed adjudicated events.
Dose level
120 mg
Route of administration:
Oral (1 tablet once daily [QD])

Primary objectives – surrogate endpoint analysis
To evaluate the efficacy of elafibranor 120 mg QD for 72 weeks versus placebo on resolution of NASH without worsening of fibrosis.

- Resolution of NASH is defined as the disappearance of ballooning and disappearance or persistence of minimal lobular inflammation (grade 0 or 1) with an overall pattern of injury not qualifying for steatohepatitis.
- Worsening of fibrosis is evaluated using the NASH Clinical Research Network (CRN) fibrosis staging system and defined as progression of at least 1 stage.

Primary objectives – long-term endpoints
To evaluate the efficacy of elafibranor 120 mg QD versus placebo on clinical outcomes described as a composite endpoint composed of death due to any cause, liver cirrhosis, and the full list of portal hypertension/cirrhosis related events:

- Liver transplantation
- MELD score ≥15
- Hepatocellular carcinoma
- the onset of:
    - variceal bleed,
    - hepatic encephalopathy,
    - spontaneous bacterial peritonitis,
    - ascites,
    - hepatorenal syndrome,
    - hepatopulmonary syndrome,
    - chronic gastrointestinal blood loss due to portal hypertensive gastropathy (provided that these lead to hospitalization or transfusion).

Key secondary objective (at surrogate endpoint analysis)
To assess histological changes after 72 weeks of treatment on the following endpoint:

- Percentage of patients with improvement of fibrosis of at least 1 stage according to NASH CRN scoring.

Other secondary objectives

- To assess histological changes after 72 weeks of treatment and follow-up biopsy on the following endpoints:
  - percentage of patients with resolution of NASH without worsening of fibrosis (follow-up biopsy)
  - percentage of patients with improvement of fibrosis of at least 1 stage according to NASH CRN scoring
  - percentage of patients with at least 1 point improvement in histological scores (NASH CRN scoring: total nonalcoholic fatty liver disease (NAFLD) activity score (NAS), steatosis, hepatic ballooning, lobular inflammation), fibrosis (NAFLD Ishak scoring system), or portal inflammation
  - percentage of patients with improvement of NAS of at least 2 points.
  - percentage of patients with at least a 1 point improvement in steatosis-activity-fibrosis (SAF) activity score
  - mean changes in NAS, steatosis, hepatic ballooning, lobular inflammation, portal inflammation, SAF activity score
  - changes in area of fibrosis by morphometry
  - mean changes in fibrosis using NASH CRN and NAFLD Ishak scoring.
- To assess the following endpoints at Week 72, and at the end of the LTTP:
  - changes in liver enzymes and liver markers
  - changes in noninvasive markers of fibrosis and steatosis
  - changes in lipid parameters
  - variation in body weight
  - changes in insulin resistance and glucose homeostasis markers
  - changes in inflammatory markers
  - changes in cardiovascular risk profile as assessed by Framingham scores
  - changes in quality of life (36-Item Short-Form Health Survey [SF-36]) questionnaire)
- To assess the onset to:
  - liver cirrhosis
  - death of any cause
  - any portal hypertension or cirrhosis related events
  - cardiovascular events
  - liver-related death events.

Exploratory objectives

- To constitute a biobank for discovery and validation of biomarkers in NASH.

Exploratory objectives for F1 group

- To explore the following endpoints in F1 patients in the exploratory group at Week 72 and at the end of the LTTP:
  - resolution of NASH without worsening of fibrosis
  - percentage of patients with at least 1 point reduction in NASH CRN fibrosis score and NAFLD Ishak score
  - percentage of patients with at least 1 point improvement in NAS, steatosis, ballooning, lobular inflammation, or portal inflammation
  - percentage of patients with improvement of NAS of at least 2 points
  - percentage of patients with at least a 1 point improvement in SAF activity score
  - mean changes in NAS, fibrosis (using NASH CRN or NAFLD Ishak scoring system), steatosis, hepatic ballooning, lobular inflammation, portal inflammation, SAF activity score
  - changes in area of fibrosis by morphometry.
- To explore the following endpoints in F1 patients at Week 72 and after the LTTP:
  - composite long-term endpoints
  - cardiovascular events
  - changes in liver enzymes and liver markers
  - changes in noninvasive markers of fibrosis and steatosis
  - changes in lipid parameters
  - variation in body weight
  - changes in insulin resistance and glucose homeostasis markers
  - changes in inflammatory markers
  - changes in cardiovascular risk profile as assessed by Framingham scores

- changes in quality of life (SF-36 questionnaire).
- To assess the tolerability and safety.

Safety secondary objectives

- To assess the tolerability and safety of once a day administration of oral doses of elafibranor 120 mg:
  - serious adverse events, adverse events, physical examination, vital signs, medical history, electrocardiogram
  - hematological parameters
  - liver markers
  - renal biomarkers (including urinalysis)
  - cardiac biomarkers
  - metabolic parameters
  - other biochemical safety markers.

Patient population:

NASH diagnosed as:

Steatohepatitis evaluated by a centrally-read liver biopsy taken within 6 months prior to Screening (if no historical biopsy is available for NASH diagnosis, a liver biopsy will be performed during the Screening Period) with:

- At least a score of 1 in each component of the NAS (steatosis scored 0-3, ballooning degeneration scored 0-2, and lobular inflammation scored 0-3).
- NAS ≥4.
- fibrosis stage of 1 or greater and below 4, according to the NASH CRN fibrosis staging system.
  For patients with fibrosis stage 1, only patients at high risk of progression will be included, meaning with a NAS ≥5 and at least 2 of the following conditions: persistent elevated alanine aminotransferase (ALT; absence of normal value of ALT within the past year), obesity defined by a body mass index (BMI) ≥30, metabolic syndrome (NCEP ATP III definition), type 2 diabetes, or homeostasis model assessment of insulin resistance (HOMA-IR) >6.

At the end of the 72-week treatment period, patients will continue in the double-blind LTTP. Patients will be monitored by notably measuring the potential appearance of cirrhosis (based on FibroScan measurement for presence of cirrhosis associated with biological and clinical assessments). If histological cirrhosis is confirmed as well as any other event listed in the long-term composite endpoint, patients will be discontinued from study.

Number of estimated randomized F2-F3 Patients: total 2022 patients (ratio 2:1)

- 674 patients in placebo group
- 1348 patients in elafibranor (GFT505) group

An additional 202 (10% of the F2-F3 patients) F1 patients at high risk of progression will be included as an exploratory arm.

Number of participating centers (planned): ~250 centers

Number of participating countries: ~25 (Belgium, France, Germany, Italy, the Netherlands, Romania, Spain, UK, Switzerland, Portugal, Denmark, Finland, Sweden, Czech Republic, Russia, Turkey, USA, Canada, Mexico, Colombia, Brazil, Argentina, Chile, Australia, South Africa)

Study duration per patient:

Estimated duration approximately 72 months, based on 456 patients experiencing a long-term composite endpoint event.

Schedule:

- Screening Period: Week -12 to Week -1 prior to Randomization.
- First Treatment Period: Week 0 to Week 72: period of treatment with elafibranor (GFT505) or placebo for 72 weeks.
- Long-term Treatment Period: Week 72 to end of study: extension of treatment with elafibranor (GFT505) or placebo (until occurrence of prespecified number of events).

Inclusion criteria:

Patients must meet all of the following inclusion criteria to be eligible for enrollment in the trial:

1. Males or females aged from 18 to 75 years inclusive at first Screening Visit.
2. Must provide signed written informed consent and agree to comply with the study protocol.
3. Females participating in this study must be of nonchildbearing potential or using highly efficient contraception for the full duration of the study and for 1 month after the end of treatment, as described below:
   - Cessation of menses for at least 12 months due to ovarian failure,

- Surgical sterilization such as bilateral oopherectomy, hysterectomy, or medically documented ovarian failure
- If requested by local IRB regulations and/or National laws, sexual abstinence may be considered adequate (the reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient)
- Using a highly effective nonhormonal method of contraception (bilateral tubal occlusion, vasectomized partner, or intra-uterine device)
- -Double contraception with barrier AND highly effective hormonal method of contraception (oral, intravaginal, or transdermal combined estrogen and progestogen hormonal contraception associated with inhibition of ovulation; oral, injectable, or implantable progestogen-only hormonal contraception associated with inhibition of ovulation; or intrauterine hormone-releasing system). The hormonal contraception must be started at least 1 month prior to Randomization.

4. Histological confirmation of steatohepatitis on a diagnostic liver biopsy by central reading of the slides (biopsy obtained within 6 months prior to Screening or during the Screening Period) with at least 1 in each component of the NAS (steatosis scored 0-3, ballooning degeneration scored 0-2, and lobular inflammation scored 0-3).
5. NAS ≥4.
6. Fibrosis stage of 1 or greater and below 4, according to the NASH CRN fibrosis staging system.
   For patients with fibrosis stage 1, only patients at high risk of progression will be included meaning with a NAS ≥5 and at least 2 of the following conditions: persistent elevated ALT (absence of normal value of ALT within the past year), obesity defined by a BMI ≥30, metabolic syndrome (NCEP ATP III definition), type 2 diabetes, or HOMA-IR >6.
7. Patients in whom it is safe and practical to proceed with a liver biopsy, and who agree to have:
   - 1 liver biopsy during the Screening Period for diagnostic purpose (if no historical biopsy within 6 months before Screening is available)
   - 1 liver biopsy after 72-weeks of treatment for assessment of the treatment effects on NASH
   - a final liver biopsy after approximately 4 years of treatment (V13), unless a liver biopsy has already been performed within the past year
   - 1 liver biopsy performed only in the case of suspicion of cirrhosis (to have a histological confirmation).
8. If a patient is treated with 1 of the following drugs: vitamin E (>400 IU/day), polyunsaturated fatty acids (>2 g/day), or ursodeoxycholic acid; a stable dose from at least 6 months prior to diagnostic liver biopsy is required.
9. For patients with type 2 diabetes, glycemia must be controlled. If glycemia is controlled by antidiabetic drugs, change in anti-diabetic therapy must follow these requirements:
   - no qualitative change 6 months prior to diagnostic liver biopsy up to Randomization (i.e., implementation of a new anti-diabetic therapy) for patients treated with metformin, gliptins, sulfonylureas, sodium/glucose cotransporter (SGLT) 2 inhibitors, glucagon-like peptide (GLP)-1 agonists, or insulin. Dose changes of these medications are allowed in the 6 months prior to diagnostic liver biopsy, except for GLP-1 agonists, which must remain on stable dose in the 6 months prior to diagnostic liver biopsy.
   - no implementation of GLP-1 agonists and SGLT2 inhibitors up to 72 weeks of treatment (V7).

   Initiation of any other antidiabetic drugs is allowed after Randomization based on treating physicians' judgment, except for glitazones which are prohibited 6 months prior to diagnostic liver biopsy until the end of treatment.

Exclusion criteria:

Patients who meet any of the following criteria will be excluded from entering the study:

1. Known chronic heart failure (Grade I to IV of New York Heart Association classification).
2. History of efficient bariatric surgery within 5 years prior to Screening, or planned bariatric surgery in the course of the study.
3. Uncontrolled hypertension during the Screening Period despite optimal antihypertensive therapy.
4. Type 1 diabetes patients.
5. Patients with hemoglobin A1c [HbA1c] >9.0%. If abnormal at the first Screening Visit, the HbA1c measurement can be repeated at the latest 2 weeks prior to Randomization. A repeated abnormal HbA1c (HbA1c >9.0%) leads to exclusion.
6. Patients receiving thiazoledinediones (glitazones [pioglitazone, rosiglitazone]) unless the drug was discontinued at least 6 months before the diagnostic liver biopsy.

7. Patients with a history of clinically significant acute cardiac event within 6 months prior to Screening such as: stroke, transient ischemic attack, or coronary heart disease (angina pectoris, myocardial infarction, revascularization procedures).
8. Weight loss of more than 5% within 6 months prior to Randomization.
9. Compensated and decompensated cirrhosis (clinical and/or histological evidence of cirrhosis). Notably, NASH patients with fibrosis stage = 4 according to the NASH CRN fibrosis staging system are excluded.
10. Current or recent history (<5 years) of significant alcohol consumption. For men, significant consumption is typically defined as higher than 30 g pure alcohol per day. For women, it is typically defined as higher than 20 g pure alcohol per day.
11. Pregnant or lactating females or females planning to become pregnant during the study period.
12. Other well documented causes of chronic liver disease according to standard diagnostic procedures including, but not restricted to:
    - positive hepatitis B surface antigen
    - positive hepatitis C Virus (HCV) RNA (tested for in case of known cured HCV infection or positive HCV Ab at Screening)
    - suspicion of drug-induced liver disease
    - alcoholic liver disease
    - autoimmune hepatitis
    - Wilson's disease
    - primary biliary cirrhosis, primary sclerosing cholangitis
    - genetic homozygous hemochromatosis
    - known or suspected hepatocellular carcinoma (HCC)
    - history or planned liver transplant, or current MELD score >12
13. Where applicable, patients not covered by Health Insurance System and/or not in compliance with the recommendations of National Law in force applicable to clinical trials.
14. Patients who cannot be contacted in case of emergency.
15. Known hypersensitivity to the investigation product or any of its formulation excipients.
16. Patients with previous exposure to elafibranor.
17. Patients who are currently participating in, plan to participate in, or have participated in an investigational drug trial or medical device trial containing active substance within 30 days or five half-lives, whichever is longer, prior to Screening.

Concomitant medications:

18. Fibrates are not permitted from 2 months before Randomization. Patients that used statins, ezetimibe, or other nonfibrate lipid lowering drugs before Screening may participate if the dosage has been kept constant for at least 2 months prior to Screening.
19. Currently taking drugs that can induce steatosis/steatohepatitis including, but not restricted to: corticosteroids (parenteral & oral chronic administration only), amiodarone (Cordarone), tamoxifen (Nolvadex), and methotrexate (Rheumatrex, Trexall), which are not permitted 30 days prior to Screening and up to end of treatment.
20. Currently taking any medication that could interfere with study medication absorption, distribution, metabolism, or excretion or could lead to induction or inhibition of microsomal enzymes, e.g., indomethacin, which are not permitted from Randomization until end of treatment.

Associated illnesses or conditions:

21. Any medical conditions that may diminish life expectancy to less than 2 years including known cancers.
22. Evidence of any other unstable or, untreated clinically significant immunological, endocrine, hematological, gastrointestinal, neurological, neoplastic, or psychiatric disease
23. Mental instability or incompetence, such that the validity of informed consent or ability to be compliant with the study is uncertain.

In addition to the above criteria, patient should not present any of the following biological exclusion criteria:

24. Positive anti-human immunodeficiency virus antibody.
25. Aspartate aminotransferase (AST) and/or ALT >10 x upper limit of normal (ULN).
26. Conjugated bilirubin > 1.50mg/dL due to altered hepatic function **Note**: Gilbert Disease patients are allowed into the study.
27. International normalized ratio >1.40 due to altered hepatic function.
28. Platelet count <100,000/mm^3 due to portal hypertension.

29. Serum creatinine levels >1.53 mg/dL in males and >1.24 mg/dL in females.
30. Significant renal disease, including nephritic syndrome, chronic kidney disease (defined as patients with markers of kidney damage or estimated glomerular filtration rate [eGFR] of less than 60 ml/min/1.73 m^2).
31. Unexplained serum creatine phosphokinase (CPK) >3 x the ULN. In case of explained elevated CPK >3 x the ULN, the measurement can be repeated prior to Randomization. In this case, retest should be performed within 1 to 2 weeks after initial test. A CPK retest >3 x ULN leads to exclusion.

Criteria for Evaluation:

Primary endpoint

Surrogate endpoint - resolution of NASH (at surrogate endpoint analysis)

To evaluate the efficacy of elafibranor 120 mg versus placebo on the resolution of NASH without worsening of fibrosis after 72 weeks of treatment.

Long-term endpoint – clinical outcomes (at final analysis)

To evaluate the efficacy of elafibranor 120 mg QD versus placebo on clinical outcomes described as a composite endpoint composed of death due to any cause, liver cirrhosis, and the full list of portal hypertension/cirrhosis related events:

- liver transplantation
- MELD score ≥15
- HCC
- the onset of:
    - variceal bleed
    - hepatic encephalopathy
    - spontaneous bacterial peritonitis
    - ascites
    - hepatorenal syndrome
    - hepatopulmonary syndrome
    - chronic gastrointestinal blood loss due to portal hypertensive gastropathy (provided that these lead to hospitalization or transfusion).

The final analysis will be performed when 456 patients experience an event listed above. This is expected to occur approximately 72 months after the first patient is randomized.

Key secondary endpoint (at surrogate endpoint analysis)

Percentage of patients with improvement of fibrosis of at least 1 stage according to NASH CRN scoring at 72 weeks.

Other secondary endpoints

- To assess histological changes after 72 weeks of treatment and follow-up biopsy on the following parameters:
    - percentage of patients with resolution of NASH without worsening of fibrosis (follow-up biopsy)
    - percentage of patients with improvement of fibrosis of at least 1 stage according to NASH CRN scoring
    - percentage of patients with at least 1 point improvement in histological scores (NASH CRN scoring: total NAS, steatosis, hepatic ballooning, lobular inflammation), fibrosis (NAFLD Ishak scoring system), or portal inflammation
    - percentage of patients improvement of NAS of at least 2 points
    - percentage of patients with at least a 1 point improvement in SAF activity score
    - mean changes in NAS, steatosis, hepatic ballooning, lobular inflammation, portal inflammation, SAF activity score
    - changes in area of fibrosis by morphometry
    - mean changes in fibrosis using NASH CRN and NAFLD Ishak scoring.
- To assess the following endpoints at Week 72, and at the end of the LTTP:
    - changes in liver enzymes and liver markers
    - changes in noninvasive markers of fibrosis and steatosis
    - changes in lipid parameters
    - variation in body weight
    - changes in insulin resistance and glucose homeostasis markers
    - changes in inflammatory markers
    - changes in cardiovascular risk profile as assessed by Framingham scores

  - changes in quality of life (SF-36 questionnaire).
- To assess the onset of:
  - liver cirrhosis
  - death of any cause
  - any portal hypertension or cirrhosis related events
  - cardiovascular events
  - liver-related death events.

Exploratory endpoints

- To constitute a biobank for discovery and validation of biomarkers in NASH.

Study Duration (planned): estimated 72 months (First Patient First Visit [FPFV]-Last patient last visit [LPLV])

- Regulatory/ethics committee submission: January 2016
- Initiation visits: March 2016 – March 2017
- Recruitment period: March 2016 – March 2018
- FPFV: March 2016
- Surrogate endpoint analysis: Q4 2018 – Q1 2019
- LPLV (LTTP): March 2022

Data Safety Monitoring Board (DSMB)

An independent DSMB will be established in order to review the progress of the study and to perform a safety data review on a regular basis during the trial to protect patient welfare and preserve study integrity. The DSMB will also review the interim analysis results and provide final recommendations regarding trial termination due to futility and adjustment of the target number of primary events.

The DSMB will consist of at least 5 experienced physicians (1 endocrinologist, cardiologist, hepatologist, oncologist, and nephrologist) and 1 statistician, all of whom will be independent of the participants in the study. The DSMB Charter will define the role, responsibilities, rules, and tasks of the DSMB.

Clinical events committee (CEC)

The CEC will conduct the adjudication of all disease progression events included in the primary composite efficacy long-term endpoint (except for histological cirrhosis), all drug-induced liver injury events, and all major cardiovascular events as defined in the CEC charter. The CEC assessment and adjudication will occur in a blinded, consistent, and unbiased manner throughout the course of a study to determine whether the endpoints meet the protocol-specified criteria.

The CEC will be comprised of 2 hepatologists, 2 cardiologists, and 1 endocrinologist all of whom will be independent of the participants in the study.

Table 1: STUDY GENERAL ASSESSMENT SCHEDULE

	Screening Period			First Treatment Period							Long-term Treatment Period		End Of Study Treatment
Visit	**SV1**[4]	**SV2**[4]	**SPV**[5]	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**Phone Visit PV1-PVn**	**V8-Vn**	**EOT**[13]
Week	*-12 to -1*		*-1*[5]	*0*[6]	*12*[6]	*24*[6]	*36*[6]	*48*[6]	*60*[6]	*72*[6]	*(every 24 weeks starting 12 weeks after V7)*[8]	*(every 24 weeks starting after V7)*[9]	*30 days after final study drug administration*
Permitted Margin				0	±1 week after V1	± 1 week after V1	± 1 week after V1	± 1 week after V1	± 1 week after V1	± 1 week after V1	± 2 weeks Compared to V7	± 2 weeks Compared to V7	± 1 week after last administration
Obtain informed consent	X												
Medical history / demographics	X												
Check inclusion / exclusion criteria	X			X[7]									
Adequate diet and lifestyle recommendations, including alcohol restrictions and smoking habits	X →	→	→	→	→	→	→	→	→	→	→	→	
Confirmation of diet and lifestyle compliance, including alcohol restrictions and smoking habits				X	X	X	X	X	X	X	X	X	X
Physical examination	X			X	X	X	X	X	X	X		X	X
Vital signs & height [1] **& weight measurement**	X			X	X	X	X	X	X	X		X	X
Waist circumference	X			X		X		X		X		X	X

	Screening Period			First Treatment Period							Long-term Treatment Period		End Of Study Treatment
Visit	**SV1**[4]	**SV2**[4]	**SPV**[5]	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**Phone Visit PV1-PVn**	**V8-Vn**	**EOT**[13]
Week	*-12 to -1*		*-1*[5]	*0*[6]	*12*[6]	*24*[6]	*36*[6]	*48*[6]	*60*[6]	*72*[6]	*(every 24 weeks starting 12 weeks after V7)*[8]	*(every 24 weeks starting after V7)*[9]	*30 days after final study drug administration*
Permitted Margin				**0**	**±1 week after V1**	**± 1 week after V1**	**± 1 week after V1**	**± 1 week after V1**	**± 1 week after V1**	**± 1 week after V1**	**± 2 weeks** Compared to V7	**± 2 weeks** Compared to V7	**± 1 week** after last administration
12-Lead ECG				X			X			X		X[10]	X
Lab evaluation (see Table 2)	X	X		X	X	X	X	X	X	X		X	X
Send sample for central histological evaluation of NASH diagnosis / change	X	X								X		X[11]	
Liver biopsy		X[4]								X		X[11]	
Phone call to patient to confirm eligibility of histology criteria			X 5										
FibroScan 2				X						X		X	
Contact the patient prior to visit 3				X	X	X	X	X	X	X		X	X
Randomization				X									
IXRS registration	X			X	X	X	X	X	X	X	X	X	X
Review prior / concomitant medication	X			X	X	X	X	X	X	X	X	X	X
Quality of life assessment				X		X		X		X		X[12]	X

	Screening Period			First Treatment Period							Long-term Treatment Period		End Of Study Treatment
Visit	**SV1**[4]	**SV2**[4]	**SPV**[5]	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**Phone Visit PV1-PVn**	**V8-Vn**	**EOT**[13]
Week	*-12 to -1*		*-1*[5]	*0*[6]	*12*[6]	*24*[6]	*36*[6]	*48*[6]	*60*[6]	*72*[6]	*(every 24 weeks starting 12 weeks after V7)*[8]	*(every 24 weeks starting after V7)*[9]	*30 days after final study drug administration*
Permitted Margin				**0**	**±1 week after V1**	**± 1 week after V1**	**± 1 week after V1**	**± 1 week after V1**	**± 1 week after V1**	**± 1 week after V1**	**± 2 weeks** Compared to V7	**± 2 weeks** Compared to V7	**± 1 week** after last administration
Adverse events	X	X		X	X	X	X	X	X	X	X	X	X
Data collection on clinical outcomes					X	X	X	X	X	X	X	X	X
Study placebo or drug dispensation				X	X	X	X	X	X	X		X	
Drug accountability					X	X	X	X	X	X	X	X	X

Abbreviations: ECG = electrocardiogram; EOT = end of treatment; IXRS = Interactive voice/web Response System; LTTP = Long-term Treatment Period; NASH = nonalcoholic steatohepatitis; PV = phone visit; QOL = quality of life; SV = Screening visit; V = visit

1. Height is measured only at visit SV1.
2. Where possible FibroScan must be done at the day of visit. Otherwise, it can be performed within 7 days around the visit date.
3. During the study, the patient should be contacted at least 1 week before the next visit as a reminder on procedures and IP return.
4. The visits to be performed during the screening period should be scheduled according to the following requirements:
   - If there are historical lab values for AST, ALT, total bilirubin and INR that are within 8 weeks to 6 months of the planned Randomization visit (V1) these results can be used as the first baseline values in case of DILI adjudication. If there are no historical lab values that meet this requirement, then SV1 and V1 must be scheduled at least 8 weeks apart.
   - The visit SV2 only occurs if no historical biopsy within 6 months before the Screening Visit is available. A screening liver biopsy and slides shipment to the central pathologist must be performed at least 4 weeks before Randomization, in order to obtain the results in time. However, in some exceptional cases, the central reading process can be expedited allowing a shorter time between SV1 or SV2 and V1. Coagulation (platelet count and PT [INR]) should be checked locally prior to this liver biopsy (according to local medical standards in each hospital).

- Randomization visit can be scheduled as soon as all the results are available to confirm the eligibility of the patients

5. Screening Phone Visit. Telephone contact for all patients at least 1 week before V1. Patients should be contacted regarding eligibility confirmation within 1 week prior to Randomization Visit V1. In case of ineligibility, the patient should be contacted as soon as possible.

6. The maximum time period between visits in the First Treatment Period is to be 96 days due to the study drug supply provided to the patient.

7. Check of all inclusion/exclusion criteria, including biological and histological criteria assessed at SV1 and SV2.

8. Phone visits every 24 weeks starting 12 weeks after V7 for safety, data collection on clinical outcomes, and IP compliance control. If any information during this phone contact requires a visit, the Investigator may decide to perform an unscheduled visit. Phone visits may also be performed at the same frequency for the follow-up of patients having permanently discontinued study drug but remaining in the study (Same information collected except IP compliance control).

9. The maximum time period between visits in the Long-term Treatment Period (LTTP) is to be 192 days due to the study drug supply provided to the patient.

10. In the LTTP the first ECG will be performed at V9 and then every 48.

11. Liver biopsy will be performed after approximately 4 years of treatment (V13) and in the case of suspicion of cirrhosis (based on FibroScan and/or clinical or biological assessment). In the case that the suspicion of cirrhosis is not confirmed by liver biopsy the patient shall remain on the study and a liver biopsy will be performed after approximately 4 years of treatment (V13, unless a biopsy has already been performed within the year). Blood sampling (coagulation tests; see Table 2) are to be performed locally before the biopsy.

12. QOL assessment questionnaire to be completed at 24 (V8), 48 (V9), and 96 (V11) weeks in the LTTP (following approximately 96, 120, and 168 weeks of treatment, respectively), and every 48 weeks thereafter.

13. EOT Visit to be performed 30 days after final study drug administration at the end of study or for any premature discontinuation (permanent study drug discontinuation or trial discontinuation).

Table 2: STUDY BIOLOGICAL ASSESSMENT SCHEDULE

Visit	Screening Period		First Treatment Period							Long-term Treatment Period	End of Study Treatment
	SV1 SB1 [6]	SB2 [7]	V1 B1	V2 B2	V3 B3	V4 B4	V5 B5	V6 B6	V7 B7	V8 to Vn B8 to Bn	EOT
Week	*-12 to -1*	*Prior to liver biopsy*	*0*	*12*	*24*	*36*	*48*	*60*	*72*	*Every 24 weeks*	*30 days after final study drug administration*
Hematology *Hemoglobin, hematocrit, RBC, WBC, differential count, platelet count, reticulocytes count, and PT (INR)*	X		X	X	X	X	X	X	X	X	X
Coagulation - local lab testing prior to liver biopsy *Platelet count, PT (INR)* 1		X							X	X [1]	
Serology *HIV ab I/II, HBsAg, and HCV Ab (positive HCV RNA in case HCV Ab >0 or known cured hepatitis C infection [2])*	X										
Screening Visit 1 - chemistry panel *HbA1c [2], fasting plasma glucose, insulin (fasting), HOMA-IR creatinine, eGFR, GGT, AST, ALT, CPK [2], alkaline phosphatase, total and conjugated bilirubin, sodium, TG, and MELD score*	X										
V1 to Vn total chemistry panel *HbA1c, fasting plasma glucose, creatinine, eGFR, GGT, AST, ALT, CPK, alkaline phosphatase, total proteins, albumin, electrolytes (sodium, potassium, chloride, calcium), uric acid, urea (BUN), total and conjugated bilirubin, hsCRP, total cholesterol, nonHDL-C, HDL-C, TG, calculated VLDL-C, ApoAI, ApoB, calculated LDL-C, and MELD score*			X [6]	X	X	X	X	X	X	X	X

Visit	Screening Period		First Treatment Period							Long-term Treatment Period	End of Study Treatment
	SV1 SB1 [6]	SB2 [7]	V1 B1	V2 B2	V3 B3	V4 B4	V5 B5	V6 B6	V7 B7	V8 to Vn B8 to Bn	EOT
Week	*-12 to -1*	*Prior to liver biopsy*	*0*	*12*	*24*	*36*	*48*	*60*	*72*	*Every 24 weeks*	*30 days after final study drug administration*
Urinalysis *albumin, creatinine, ACR, and microscopic analysis* *α1 microglobulin*, β-NAG,* N-Gal*, IL-18*, KIM-1*,*			X	X	X	X	X	X	X	X	X
Urinalysis (dipstick) *Specific gravity, pH, protein, glucose, ketones, bilirubin, urobilinogen, blood, nitrite, and leukocytes*	X		X	X	X	X	X	X	X	X	X
Urinary pregnancy tests [3]	X		X	X	X	X	X	X	X	X	X
Inflammatory markers *Fibrinogen, and haptoglobin*			X		X		X		X	X	X
Other Liver markers *CK18 (M65 & M30), adiponectin, ferritin, FGF19 & FGF21, alpha2 macroglobulin, hyaluronic acid, PIIINP, TIMP-1, and CHI3L1* [4]			* [4]		*		*		* [4]	* [4]	*
Calculated fibrosis & steatosis index *Fibrotest, ELF, NAFLD Fibrosis score, Steatotest, FLI, Fibrometre S, and FIB-4*			*		*		*		*	*	*
Other safety markers *Homocysteine, NT-ProBNP, troponin-T, and cystatin C*			*		*		*		*	*	*
Special glycemic and other lipid parameters *Insulin(fasting), HOMA-IR, Fructosamine, C-peptide, FFA, small dense LDL, ApoAII, Apo CIII, and Apo E*			*		*		*		*	*	*

Visit	Screening Period		First Treatment Period							Long-term Treatment Period	End of Study Treatment
	SV1 SB1 [6]	SB2 [7]	V1 B1	V2 B2	V3 B3	V4 B4	V5 B5	V6 B6	V7 B7	V8 to Vn B8 to Bn	EOT
Week	*-12 to -1*	*Prior to liver biopsy*	*0*	*12*	*24*	*36*	*48*	*60*	*72*	*Every 24 weeks*	*30 days after final study drug administration*
Sampling for additional parameters *Whole blood [5], plasma, and serum bank*	* [5]		*	*	*	*	*	*	*	*	*

X = results available within 2 working days (routine analysis) * = batch analysis

Abbreviations Ab = antibody; ACR = albumin–creatinine ratio; Ag = antigen; ALT = alanine aminotransferase; Apo = apolipoprotein; AST = aspartate aminotransferase; β-NAG = N-acetyl-β-D-glucosaminidase; BUN = blood urea nitrogen; B = biological assessment Visit; CHI3L1 = chitinase-3-like protein 1; CK18 = cytokeratin 18; CPK = creatine phosphokinase; eGFR = estimated glomerular filtration rate; ELF = enhanced liver fibrosis; EOT = end of study treatment; FFA = free fatty acid; FGF = fibroblast growth factor; FIB-4 = fibrosis 4 score; FLI = fatty liver index; GGT = gamma-glutamyl transferase; HbA1c = hemoglobin A1c; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HDL-C = high density lipoprotein-C; HIV = human immunodeficiency virus; HOMA-IR = homeostasis model assessment of insulin resistance; hsCRP = high-sensitivity C-reactive protein; IL-18 = interleukin 18; INR = international normalized ratio; KIM-1 = kidney injury molecule-1; LDL-c = low density lipoprotein-C; MDRD = modification of diet in renal disease; MELD = model end stage liver disease; NAFLD = nonalcoholic fatty liver disease; N-Gal = neutrophil gelatinase-associated lipocalin; NT-ProBNP = N-terminal of the prohormone brain natriuretic peptide; PIIINP = type III procollagen peptide; PT = prothrombin time; TIMP-1 = tissue inhibitors of metalloproteinases 1; RBC = red blood cell; SB = Screening biological assessment Visit; SV = Screening Visit; TG = triglyceride; VLDL-C = very low density lipoprotein-C; V = Visit; WBC = white blood cell.

1. Coagulation (platelet count and PT [INR]) should be checked prior to any liver biopsy (according to local medical standards in each hospital). To be done through a local laboratory. Liver biopsy will be performed after 72 weeks (V7) and after approximately 4 years of treatment (V13) and in the case of suspicion of cirrhosis (based on FibroScan and/or clinical or biological assessment). In the case that the suspicion of cirrhosis is not confirmed by liver biopsy the patient shall remain on the study and a liver biopsy will be performed after approximately 4 years of treatment ([V13] unless a biopsy has already been performed within the past year).

2. Upon receipt of the results of the biological assessment performed at SV1, retesting or additional testing may be needed during the Screening Period:

- CPK can be repeated prior to Randomization (V1) within 1 to 2 weeks after initial test.
- HbA1c can be repeated prior to Randomization (V1), at the latest 2 weeks prior to planned Randomization.
- HCV RNA can be tested, at SV1 in case of known cured hepatitis c infection, or in case of positive HCV Ab at SV1, at a retest screening visit at the latest 2 weeks prior to the planned Randomization (V1).

3. Dipstick at site for WOCBP only. In addition, home pregnancy tests are to be performed by WOCBP every 4 weeks from V1 (see Table 1 and Figure 2).

4. CHI3L1 to be tested only at V1, V7, and at the time of 4 years biopsy (V13).

5. Whole blood sample will be only taken at SV1 while plasma and serum samples are to be taken at every visit **ONLY** for patients who have signed the pharmacogenomic and biomarker ICF.

6. If no historical values of AST, ALT, total bilirubin and INR meeting the requirements of within 8 weeks to 6 months of planned randomization visit (V1) are available, then SV1 and V1 must be scheduled at least 8 weeks apart in order to have 2 consecutive values for DILI adjudication. In any case, the visits should be scheduled in order to obtain the needed results prior to the randomization.

7. SB2, additional visit in the Screening Period if required for coagulation prior to liver biopsy.

Figure 1: STUDY DURATION AND VISIT SCHEDULE

Figure 2: PREGNANCY TESTING SCHEDULE FOR WOMEN OF CHILDBEARING POTENTIAL

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AASLD	American Association for the Study of Liver Diseases
ACR	albumin–creatinine ratio
ADR	adverse drug reaction
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	Analysis of Covariance
ApoAI	apolipoprotein AI
ApoAII	apolipoprotein AII
ApoB	apolipoprotein B
ApoCIII	apolipoprotein CIII
AST	aspartate aminotransferase
AT	aminotransferase
ATP	Adult Treatment Panel
BMI	body mass index
BP	blood pressure
BUN	blood urea nitrogen
Bx	biological assessment visit
CA	competent authorities
CEC	Clinical Events Committee
CFR	Code of Federal Regulations
CPK	creatine phosphokinase
CRN	Clinical Research Network
CRO	Clinical Research Organization
CRP	C-reactive protein
CSR	Clinical Study Report
CYP	cytochrome P450
DDI	drug-drug interaction
DILI	drug-induced liver injury
DSMB	Data Safety Monitoring Board
EASL	European Association for the Study of the Liver
ECG	electrocardiogram
eCRF	electronic case report form
EES	efficacy evaluable sample
eGFR	estimated glomerular filtration rate
EOS	end of study
EOT	end of study treatment
FDA	Food and Drug Administration
FFA	free fatty acid
FIB-4	fibrosis 4 score
FITT	full intent-to-treat set
FLI	fatty liver index
FPFV	first patient first visit
FSS	full safety set
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase

GLP1	glucagon-like peptide 1
HbA1c	hemoglobin A1c
HBsAg	hepatitis B surface antigen
HCC	hepatocellular carcinoma
HCV	hepatitis C Virus
HDL-C	High-density lipoprotein cholesterol
HIV	human immunodeficiency virus
HOMA-IR	homeostasis model assessment of insulin resistance
hPPAR	human peroxisome proliferator-activated receptor
HRT	Hormonal replacement therapy
HSC	hepatic stellate cells
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
INR	international normalized ratio
IP	investigational product
IR	insulin resistance
IRB	Institutional Review Board
ITT	intent-to-treat
IXRS	Interactive Voice/Web Response System
LDL-C	Low-density lipoprotein cholesterol
LPLV	last patient last visit
[redacted]	[redacted]
LTTP	Long-term Treatment Period
M2	anti-inflammatory macrophages
MedDRA	Medical Dictionary for Regulatory Activities
MELD	model end stage liver disease
NAFLD	nonalcoholic fatty liver disease
NAS	NAFLD Activity Score
NASH	nonalcoholic steatohepatitis
NCEP ATP III	National Cholesterol Education Program's Adult Treatment Panel III
PD	pharmacodynamics
PK	pharmacokinetics
PPAR	peroxisome proliferator-activated receptor
PPS	per protocol set
PT	prothrombin time
PUFA	polyunsaturated fatty acids
QD	once daily
QTc	corrected QT
SADR	serious adverse drug reaction
SAE	serious adverse event
SAF	steatosis, activity, and fibrosis
SAP	Statistical Analysis Plan
SBx	screening biological assessment visit
SF-36	36-Item Short-Form Health Survey
SGLT2	sodium/glucose cotransporter 2
SOP	Standard Operating Procedure

SS	safety set
SUSAR	suspected unexpected serious adverse reactions
SVx	Screening Visit x
TLC	therapeutic lifestyle change
TNFα	Tumor Necrosis Factor-alpha
ULN	upper limit of normal
UV-LLNA	UV- Local Lymph Node Assay
Vx	Visit x
WOCBP	women of childbearing potential

1. INTRODUCTION

1.1. NONALCOHOLIC STEATOHEPATITIS

Nonalcoholic fatty liver disease (NAFLD) is a spectrum of disorders characterized by excessive fat accumulation in the liver (steatosis). Nonalcoholic steatohepatitis (NASH) defines a subgroup of NAFLD where steatosis coexists with hepatocyte injury and inflammation (steatohepatitis), with or without fibrosis.

Nonalcoholic steatohepatitis is considered by the European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Diseases (AASLD) as an increasing public health issue owing to its close epidemiological association with the worldwide epidemic of obesity and type 2 diabetes.

The prevalence of NAFLD in the general population assessed by ultrasonography is 20% to 30% in Europe. A similar prevalence of 15% to 25% was documented histologically by postmortem studies. A high prevalence of histological NAFLD has been described in apparently healthy liver donors: 12% to 18% in Europe and 27% to 38% in the US. Furthermore, with a sensitive technique such as magnetic resonance spectroscopy, 34% have NAFLD.

Interestingly, 39% of newly diagnosed cases of chronic liver disease had NAFLD, making NASH one of the top causes of liver diseases in Western countries. Using the histological definition of NASH, recent studies have shown a high prevalence of NASH among NAFLD cases: 43% to 55% in patients with increased aminotransferases (ATs), 49% in morbidly obese patients, and 67% in a subset of patients with incident chronic liver disease. Finally, in apparently healthy liver donors the prevalence of NASH ranges from 3% to 16% in Europe and from 6% to 15% in the US.

The commonest cause of NASH is primary NAFLD-associated insulin resistance and its phenotypic manifestations, namely excess weight/obesity, visceral obesity, type 2 diabetes, hypertriglyceridemia, and arterial hypertension. A causal association has been suggested by longitudinal studies showing a chronological association between the progression of insulin resistance, the metabolic syndrome, and the occurrence of NAFLD/NASH.

1.2. PATHOPHYSIOLOGICAL PROCESS OF NONALCOHOLIC STEATOHEPATITIS

A widely described model suggests that the development of NAFLD into NASH requires several 'hits' or insults.[1,2] According to this model, increased hepatic levels of free fatty acid (FFA) consequent to impaired insulin sensitivity in the liver and peripheral tissues may serve as the first hit. The increased hepatocyte FFA load would further increase insulin resistance (IR), steatosis, oxidative stress with lipid peroxidation, endoplasmic reticulum stress, resulting in inflammatory cell accumulation and activation into the liver (second hit). This finally leads to hepatocyte growth arrest or apoptosis, which activates hepatic progenitor cells and associated bile ductular proliferations, cells that initiate inadequate repair by producing a diverse range and high concentrations of profibrogenic cytokines and growth factors that activate hepatic stellate

cells (HSC) and perivascular or portal fibroblasts. The activated HSC themselves can release chemotactic factors that recruit inflammatory cells, creating a deleterious feedback inflammatory loop that leads to fibrogenesis. Collagen and other extracellular matrix components accumulate within the liver, which may result in distortion of the hepatic architecture and finally cirrhosis. Thus, in this "multiple-hit" model IR can be considered as the first step on the pathogenic road leading to NASH, fibrosis and cirrhosis.

However, this "multiple-hit" model has been recently challenged by data suggesting that mechanisms that can drive disease progression can also induce steatosis. Oxidative stress and gut flora/cytokines can induce steatosis as well as necroinflammation and fibrosis. Free fatty acids can initiate hepatocyte apoptosis in addition to being esterified to triglycerides. Endoplasmic stress can also lead to steatosis, oxidative stress, and apoptosis. Since all these mechanisms are important in obesity and IR, it would seem likely that they are the true "first hits" leading to increased hepatic FFA flux and oxidative-, endoplasmic reticulum-, and cytokine-mediated stress that result in both steatosis and progressive liver damage. Steatosis should therefore be considered part of the liver's early "adaptive" response to stress, rather than a first hit in disease progression. Accordingly, while in some situations its severity may act as a biomarker of ongoing injurious and fibrotic mechanisms resulting in disease progression, it should not be considered a sole therapeutic target. Instead attention should be paid on the mechanisms of cellular injury and fibrosis – the "second hits."

Oxidized by-products are harmful adducts that can cause liver injury, resulting in subsequent fibrosis.[3] Lipid peroxidation and oxidative stress up-regulate liver fibrosis via activation of stellate cells and increased production of Transforming Growth Factor-beta.4 Over expression of uncoupling proteins has been associated with a reduction in generation of reactive oxygen species and Kupffer cell activation, which might attenuate injury in NAFLD. In addition to insulin resistance, several authors have shown that leptin contributes to an insulin-resistant state and might even stimulate fibrogenesis in animal models of NAFLD.5

Inflammatory mediators have been implicated in the progression of NAFLD and are the focus for new therapeutics. Pro-inflammatory transcription factors such as Nuclear Factor kappa B (NF-κB) are often elevated in patients with NASH.6 Adiponectin decreases fatty acid oxidation and inhibits hepatic gluconeogenesis.7 Both human and mouse models have demonstrated that lower adiponectin levels are associated with increased severity of hepatic inflammation.[8,9] Tumor Necrosis Factor (TNF)α is an inflammatory mediator largely produced by macrophages, but also elaborated by other cells including adipocytes and hepatocytes.[1,10] Elevated levels of TNFα have been detected in obese patients with insulin resistance and NASH.[11,12] TNFα-mediated hepatic injury results from inhibition of mitochondrial electron transport and release of reactive oxygen species that stimulate lipid peroxidation.[10]

Recently, scientists have focused on the role of Kupffer cells in the pathogenesis of NAFLD. Kupffer cells are the resident macrophages of the liver and function in both innate and adaptive immunity as active phagocytosing agents and antigen-presenting cells (via toll-like receptors) to T-cells. Finally, the

proapoptotic gene Bax is upregulated in patients with NASH and alcoholic liver disease.[13] Additionally, caspase levels, by-products of cellular apoptosis, are also increased in these groups of patients.

1.3. ELAFIBRANOR: RATIONALE FOR A MIXED PPAR ALPHA/DELTA AGONIST IN NASH

The GENFIT drug candidate, elafibranor, and its main active circulating metabolite, GFT1007, are dual peroxisome proliferator-activated receptor (PPAR)α/δ modulators with preferential activity on PPARα over PPARδ (about fivefold more potent on human PPAR [hPPAR]α than on hPPARδ). The PPARδ properties of elafibranor and GFT1007 have been demonstrated in both human skeletal muscle cells (a pure PPARδ response) and human hepatocytes (a mixed PPARα/δ response).

The PPARα receptors are most prominently expressed in the liver and can be activated by drugs of the fibrate class. Activation results in increased uptake and oxidation of FFAs, increased triglyceride hydrolysis and upregluation of apolipoprotein (Apo)A-I and ApoA-II. The net effect is fatty acid oxidation, decrease in serum triglycerides, a rise in high-density lipoprotein cholesterol (HDL-C) levels, and an increase in cholesterol efflux. The PPARα activation has also anti-inflammatory effects via inhibition of COX2, IL-6, and C-reactive protein (CRP). Some PPARα compounds have proved their effectiveness in animal models like Methionine-Choline-Deficient diet model or CCl4 in reducing the steatosis. However, clinical trials with fibrates in human NASH have been unimpressive. For example in a pilot study, 12 months treatment with clofibrate in 16 patients with NASH and elevated triglycerides had no impact on liver enzyme elevation or triglycerides levels.[14]

The PPARδ appears to be a powerful metabolic regulator, with actions on fat, skeletal muscle, liver, and heart. Its activation enhances fatty acid transport and oxidation, improves glucose homeostasis via improved insulin sensitivity and inhibition of hepatic glucose output, turns off macrophage inflammatory responses, and dramatically increases circulating HDL-C levels. Thus selective PPARδ agonists have the potential to target multiple components of the metabolic syndrome, including obesity, dyslipidemia, hypertriglyceridemia insulin resistance, and probably NASH.

Accordingly, PPARδ ligands also show promise in chronic inflammatory models of hepatotoxicity.[15] Notably, biomarkers of liver toxicity, including serum alanine aminotransferase (ALT), hepatic TNFα, TNF-like weak inducer of apoptosis receptor, were all higher in carbon tetrachloride-treated PPARδ knockout mice compared to wild-type mice. GW0742 reduced serum ALT, TNFα, S100A6, MCP1, and TNF-like weak inducer of apoptosis receptor in wild-type mice, but not PPARδ knockouts.

Finally, in a short clinical trial, a pure PPARδ agonist, GW501516, has demonstrated efficacy on liver fat content while improving insulin resistance and decreasing γGT.[16]

Considering the emerging role of Kupffer cells in the pathogenesis, 2 recent publications identified PPARδ as a crucial signaling receptor controlling the phenotypic switch between classical pro-inflammatory and alternative anti-inflammatory (M2) macrophages.[17,18] These studies demonstrate that PPARδ encourages

macrophages toward the alternative M2 phenotype, which improves fatty acid metabolism, insulin sensitivity, and suppresses inflammation. The finding raise the possibility that small molecule agonist of PPARδ may be effective therapeutic targets for the treatment of chronic inflammation in the liver.

The match between the activation of PPARα and PPARδ in the liver may thus improve NASH. Accordingly, in several well-established experimental models of NAFLD/NASH and liver fibrosis, treatment with elafibranor confers liver protection both in preventive and therapeutic approaches on established pathologies. These effects have been demonstrated through plasma and hepatic markers, as well as liver macro- and micro- histological examination. These studies have shown that elafibranor acts on several mechanisms involved in NASH pathogenesis: steatosis, inflammation, and fibrosis pathways. Complementary studies have demonstrated that both PPARα-dependent and PPARα-independent mechanisms participate in the beneficial effects of elafibranor on NAFLD/NASH.

1.4. SUMMARY OF NONCLINICAL STUDIES

1.4.1. Pharmacology

Besides hepatoprotection, the efficacy of elafibranor has been assessed in numerous pharmacological preclinical models of metabolic disorders. Briefly, in experimental models of type 2 diabetes, elafibranor has insulin-sensitizing and glucose lowering properties. In db/db mice, a 28-day treatment with elafibranor produced a dose-dependent decrease in fasting plasma glucose and glycated hemoglobin (HbA1c), comparable to the effect of rosiglitazone. However, in contrast to the PPARγ reference agonist, elafibranor did not increase plasma adiponectin, thus ruling out a PPARγ -mediated effect on adipose tissues. Similarly, in ob/ob mice, elafibranor ameliorated plasma glucose and insulin levels without modulating plasma adiponectin or inducing PPAR target genes in adipose tissues.

Besides its effects on NAFLD/NASH and type 2 diabetes, oral treatment with elafibranor in a mouse model of dyslipidemia potently reduced plasma triglycerides and total cholesterol through the induction of PPARα target genes in the liver and by reduction of ApoCIII gene expression. In parallel, elafibranor increased plasma HDL-C levels more potently than the PPARα reference compound fenofibrate. The chronic treatment of these mice fed a high fat diet with elafibranor prevented the development of atherosclerotic plaques in the aorta.

1.4.2. Safety pharmacology

Any potential effect on the cardiovascular, respiratory, and central nervous system has been assessed and no safety issue was identified.

1.4.3. Absorption/distribution/metabolism/excretion studies (ADME)

In animal studies, elafibranor was well and rapidly absorbed although absolute bioavailability was moderate (about 20% to 40%). Elafibranor is extensively metabolized and the activity is mainly carried by

the active metabolite GFT1007. In rat and dog, maximal plasma concentrations and exposure for both elafibranor and GFT1007 linearly increase with the dose after single or repeated administrations. Elafibranor and its metabolites are rapidly cleared from the plasma and they are totally excreted by both fecal and renal route within 48 hours. In the rat elafibranor and/or its metabolites are rapidly excreted into the bile and undergo an extensive entero-hepatic cycle giving support for liver targeting of elafibranor and/or GFT1007. The distribution study in the rat supports the liver targeting of elafibranor and/or its metabolites.

In vitro elafibranor does not inhibit cytochrome p450 (CYP)1A2, CYP3A4, and CYP2D6 with moderate inhibition of CYP2C9 and weak inhibition of CYP2C8, CYP2C19, and CYP4A11. GFT1007 does not produce any inhibition of the CYP450 isoforms 1A2, 3A4, 2C19, and 2D6, and only weak inhibition of CYP2C8 and CYP2C9. Both molecules also show weak inhibition of CYP3A4/5, but only with midazolam as substrate. Thus, the risk of drug-drug interaction due to an inhibition of the main cytochromes involved in drug metabolism should be limited. Potential interaction with CYP2C9 metabolized drugs has been assessed through a clinical study (GFT505-112-8) designed to evaluate potential pharmacokinetic (PK) interaction of elafibranor 120 mg administered for 14 days alone or with a single administration of warfarin. This study demonstrated that elafibranor administration did not affect the PK profile of warfarin (R-warfarin and S-warfarin).

A protein binding study showed that elafibranor and GFT1007 were highly bound to human serum albumin. The risk of drug-drug interaction due to albumin binding should be limited since this binding is not saturable.

In vitro studies have been performed to determine whether elafibranor (GFT505) and it principal metabolite GFT1007 are substrates and/or inhibitors of major drug transporters, in order to assess the potential for drug-drug interaction (DDI). Based on the results of the OATP1B3 transporter inhibition assay, elafibranor (GFT505) has recently been assessed in a follow-up clinical DDI study with the OATP1B3-sensitive substrate, atorvastatin.

For the other drug transporters studied, the interaction observed does not require follow-up studies based on current regulatory guidance.

The metabolic stability and metabolism pathways of elafibranor (GFT505) have been studied on liver microsomes and in primary hepatocytes from rat, dog, mouse, monkey, and human. There was no evidence of the formation of unique human metabolites or metabolites formed at disproportionately higher levels in human hepatocytes than in any other species.

An in vivo study has been performed to compare the bioavailability of ^{14}C-GFT505 in the rat, dog, minipig, and monkey. This study showed that in all species ^{14}C-GFT505 is rapidly absorbed, although absolute bioavailability was moderate (about 20% to 40%).

1.4.4. Toxicology

1.4.4.1. Mutagenicity and genotoxicity

The toxicology program performed according to International Council for Harmonisation (ICH) guidelines demonstrates that elafibranor has no genotoxic or mutagenicity potential.

1.4.4.2. Acute toxicity

According to acute toxicity studies results, it can be concluded that elafibranor is extremely safe when administered as single oral doses in rat and mouse, since no sign of toxicity was detected up to the dose of 1000 mg/kg.

1.4.4.3. Repeated dose toxicity studies

The safety of elafibranor has been assessed in multiple preclinical toxicology studies with repeated-dose oral administration for up to 6 months in rats and 12 months in monkeys. Moreover, two-year repeated-dose carcinogenicity studies in mice and rats have been completed.

The only consistent safety concern raised by these studies is the expected PPARα-associated hepatomegaly, hepatocellular hypertrophy, and liver carcinoma in rodent species (mice and rats). However, it is well known that, compared to nonhuman primates and humans, rodents are highly sensitive to PPARα agonist induced peroxisome proliferation and associated liver side effects. Thus, available information on this class of drug which includes marketed fibrates together with the lack of any liver side effects in monkeys treated with high doses of elafibranor for 1 year support the nonrelevance to human.[19] Overall, these studies did not reveal any other safety issues up to the highest doses tested. Notably, elafibranor did not have any of the known PPARγ-related concerns such as excess in weight gain, hemodilution, edema, cardiomegaly, adiponectin induction, or urinary bladder carcinoma.

1.4.4.4. Phototoxicity studies

The phototoxic potential of elafibranor has been assessed by the in vitro 3T3 NRU phototoxicity test and the UV- Local Lymph Node Assay (LLNA) test in mice. Elafibranor (GFT505), but not its major metabolite GFT1007, showed UVA-dependent cytotoxicity in vitro. The UV-LLNA test was performed in mice with oral dosing for 3 days at up to 800 mg/kg/day elafibranor. Although a very conservative no observed effect level (NOAEL) was set at 400 mg/kg/day based on isolated findings at the highest dose, it is considered that data are more in favor of an absence of phototoxic effect, given the tissue distribution of elafibranor (GFT505), and absence of phototoxicity signal in the clinical studies.

1.5. CLINICAL STUDIES

1.5.1. Phase I program

A Phase I program to assess the safety and tolerability as well as the PK profile of elafibranor has been conducted through 12 clinical trials, one of them ongoing. A total of 621 volunteers were randomized in these studies performed in Phase I centers, including 549 healthy lean subjects, 60 overweight or obese subjects, and 12 patients with type 2 diabetes.

The plasma concentrations of elafibranor and GFT1007 were determined using validated high-performance liquid chromatography tandem mass spectrometry methods. The PK parameters were calculated using a noncompartmental analysis.

In healthy volunteers, the PK of elafibranor and GFT1007 after single administration of elafibranor at rising dose levels were assessed in 2 distinct double-blind, placebo-controlled randomized trials from 10 to 120 mg (GFT505-106-1 and GFT505-108-4). The PK of elafibranor and GFT1007 after repeated doses of elafibranor at rising dose levels were assessed in 3 distinct double-blind, placebo-controlled randomized trials: GFT505-106-2 (5, 10, 20, and 30 mg/d), GFT505-108-4 (40, 60, 80, and 100 mg/d) and GFT505-113-9 (300 and 360 mg/d).

In overweight/obese but otherwise healthy volunteers, the PK of elafibranor and GFT1007 after single administration of elafibranor at rising dose levels from 180 to 300 mg were assessed in a double-blind, placebo-controlled randomized trial (GFT505-111-7). In the same trial, the PK of elafibranor and GFT1007 after repeated doses of elafibranor at dose levels from 120 to 240 mg, were assessed in overweight/obese but otherwise healthy volunteers. Another part of this trial assessed the PK of elafibranor and GFT1007 after repeated doses of elafibranor at 180 mg in type 2 diabetic patients.

The food effect on PK of elafibranor and GFT1007 was assessed in healthy volunteers at the dose of 30 mg elafibranor in a Phase I, randomized, crossover trial (GFT505-106-1).

The PK of elafibranor and GFT1007 obtained after administration of the different formulations used throughout clinical evaluation of elafibranor were compared in dedicated clinical trials in healthy volunteers: GFT505-108-3, GFT505-111-7, and GFT505-115-12. Comparable relative bioavailability was demonstrated.

The lack of PK DDI between elafibranor (80 mg/d) and Simvastatin has been verified (GFT505-109-5).

The lack of effect of a concomitant administration of sitagliptin on elafibranor PK has been verified (GFT505-109-6).

The lack of effect of elafibranor administration (120 mg/d) on the PK and pharmacodynamics (PD) of warfarin has been verified (GFT505-112-8).

The lack of effect of elafibranor administration (180 mg/d) on the PK and PD of atorvastatin has been verified (GFT505-115-11).

The study GFT505-113-9 evaluated the effect of multiple oral doses of elafibranor on the QT/corrected QT (QTc) interval compared to placebo with moxifloxacin (400 mg in single oral dose) as a positive control, in healthy male and female volunteers. No effect of elafibranor on QT/QTc interval at both therapeutic and supratherapeutic doses for 14 days was observed.

The excretion balance of radiocarbon (i.e., the sum of ^{14}C-labeled elafibranor and its ^{14}C-labeled metabolites) and the metabolite profiling and PK of elafibranor after a single oral dose of 120 mg ^{14}C-labeled elafibranor have been assessed (GFT505-114-10). Most of the radiocarbon was excreted in feces (77.1%) and urine (19.3%), giving a recovery of 96.3% of the administered dose. The metabolite profile was assessed in plasma, urine, and feces, and did not highlight any new Phase I metabolite but allowed the identification of new glucuronated metabolites, one of them being the main urinary metabolite (12% of the administered dose).

Part of the study GFT505-115-12 is still ongoing. The objective is to assess the dose linearity after single oral administration of 120, 180, and 240 mg of elafibranor, and the time dependency of the PK parameters after single and multiple oral administration of therapeutic dose of elafibranor.

1.5.2. Phase II program

A Phase II program was initiated to assess the safety, and efficacy profile of elafibranor in patients suffering from cardiometabolic disorders. To date, 5 Phase IIa pilot trials have been completed in which 297 patients were randomized. A Phase IIb trial has recently been completed (Clinical Study Report [CSR] not yet available), and evaluated the efficacy and safety of elafibranor 80 mg and 120 mg on steatohepatitis in 274 patients with NASH.

A Phase IIa pilot study (GFT505-207-1) was first conducted to evaluate the efficacy, safety, and tolerability of elafibranor at 30 mg/d for 28 days in patients with Fredrickson type IIb dyslipidemia. Thirty-seven randomized patients received elafibranor 30 mg (24 patients) or placebo (13 patients) over a 28-day treatment period. Although improvements were observed on primary lipid parameters, these trends were not statistically significant versus placebo.

The Phase IIa study (GFT505-208-3) assessed efficacy and safety in men and postmenopausal women with atherogenic dyslipidemia (high triglycerides, low HDL-C) and abdominal obesity treated once a day for 28 days with 80 mg/d of elafibranor. Ninety-four patients were randomized: 63 patients in the elafibranor 80 mg/d arm and 31 patients in the placebo arm.

The Phase IIa study (GFT505-209-4) assessed efficacy and safety in patients treated for 35 days with elafibranor at 80 mg/d. This study targeted patients with impaired fasting glucose and impaired glucose

tolerance associated with abdominal obesity. Forty-seven patients were randomized: 23 patients in the elafibranor 80 mg/d arm and 24 patients in the placebo arm.

The Phase IIa study GFT505-210-5 assessed efficacy and safety in patients with type 2 diabetes mellitus. Patients were treated once a day for 12 weeks with 80 mg/d of elafibranor. Ninety-seven patients were randomized: 50 patients in the elafibranor 80 mg/d arm and 47 patients in the placebo arm.

The Phase IIa study (GFT505-210-6) was designed to evaluate the safety and efficacy of elafibranor on hepatic and peripheral insulin sensitivity using the gold standard glucose clamp technique in male patients with homeostasis model assessment of insulin resistance (HOMA-IR) >3 and abdominal obesity. Patients were treated once daily (QD) with 80 mg/d of elafibranor or placebo for 8 weeks in a crossover design. In this study, after 8 weeks of treatment, elafibranor significantly improved the response of the liver to insulin action. Indeed, at the first level of insulin perfusion, the insulin-induced decrease in hepatic glucose production was -49±4% after elafibranor versus -34±4% after placebo (p=0.0016). The insulin sensitivity of the muscles and other peripheral tissues measured at the second level of insulin perfusion was also increased by 28% with a significant effect on the glucose infusion rate (3.69±0.31 mg/kg/min after elafibranor versus 3.21±0.31 mg/kg/min after placebo, p=0.048). Moreover, at the end of the treatment period, elafibranor significantly lowered the FFA levels measured at the first insulin level (FFA 0.21 mEq/L after elafibranor versus 0.27 mEq/L after placebo, p=0.006).

The favorable effect of elafibranor on insulin sensitivity and glucose homeostasis was also observed in studies GFT505-209-4 and GFT505-210-5. In prediabetic patients with impaired fasting glucose, impaired glucose tolerance, and abdominal obesity (study GFT505-209-4), treatment with elafibranor 80 mg/d for 28 days led to a significant decrease in fasting plasma glucose (-5%, p=0.04), fasting plasma insulin (-25%, p=0.009), and consequently improvement of the insulin resistance index (HOMA-IR: -31%, p=0.027). In diabetic patients treated for 3 months with 80 mg/d of elafibranor (study GFT505-210-5), oral glucose tolerance test-derived parameters, including area under the time-concentration curve for glycemia, insulinemia and FFA levels, significantly improved.

In all Phase IIa studies, patients treated with elafibranor at 80 mg/d for 1 to 3 months consistently experienced an improvement of the plasma lipid profile, with significant reduction of triglycerides (-20% to -35%), reduction in low-density-lipoprotein cholesterol (LDL-C) (-10% to -15% in prediabetic, insulin-resistant and diabetic patients) and increase in HDL-C (+10% in patients with atherogenic dyslipidemia). In addition, elafibranor treatment consistently increased the anti-atherogenic apolipoproteins (ApoAI and ApoAII) while reducing the pro-atherogenic apolipoproteins (ApoB, ApoCIII, ApoE).

In all Phase IIa studies, elafibranor treatment at 80 mg/d for 1 to 3 months also led to favorable reductions in inflammatory markers. Reduced haptoglobin levels were observed in all Phase IIa clinical trials with elafibranor, with the greatest effect obtained after 3 months of treatment in diabetic patients (-20% in the elafibranor group versus +6% in the placebo group, p<0.001). Similarly, fibrinogen levels were consistently decreased by approximately 10% in all Phase IIa clinical trials with elafibranor, and

high-sensitivity CRP levels were lowered after 3 months of treatment in diabetic patients (-17% in the elafibranor group versus +52% in the placebo group).

Finally, beneficial effects of elafibranor on liver function were consistently observed in all Phase IIa clinical trials of patients treated for 1 to 3 months with 80 mg/d elafibranor. Significant reductions in circulating levels of gamma-glutamyl transferase (GGT) were observed in each study and reached up to -29% in elafibranor treated groups compared to placebo. In addition, in insulin-resistant patients, elafibranor treatment induced a significant reduction in ALT (-20% compared to placebo), while the level of aspartate aminotransferase (AST) was unchanged.

A Phase IIb study in NASH patients (GFT505-212-7) included 274 patients and involved a total of 56 centers in the US and in multiple European countries (France, Belgium, The Netherlands, Italy, UK, Germany, Spain, and Romania). The study evaluated the efficacy and safety of elafibranor at 80 and 120 mg QD for 52 weeks versus placebo in reversing histological steatohepatitis without worsening of fibrosis.

The study analyses showed that elafibranor at 120 mg demonstrates efficacy on the resolution of NASH without worsening of fibrosis in patients with an active disease (NAFLD Activity Score [NAS] score ≥4). Importantly, elafibranor at 120 mg concomitantly improved the cardiometabolic risk profile of NASH patients by decreasing plasma triglycerides, total and LDL-C, increasing HDL-C, and improving inflammation, insulin resistance and glucose homeostasis.

The good safety profile of elafibranor was confirmed in this study. Elafibranor was well tolerated, at both doses. From the start to end of the study, regular safety reviews did not generate any comment or additional request from the Data Safety Monitoring Board (DSMB). The most frequent and expected adverse events were of gastrointestinal nature. Clinical adverse events were generally mild to moderate in severity and were similar in the placebo and treated groups for the most frequently reported treatment-related AEs. Leukocyturia, hypoglycemia, and diabetes mellitus inadequate control were more frequent in elafibranor arms as well as cutaneous rash, arthralgia, decrease in appetite, dizziness and renal impairment which were only reported in the elafibranor treated groups. Serious adverse events (SAE) were reported in 27 patients treated with elafibranor (13 with elafibranor 80 mg/d and 14 with elafibranor 120 mg/d). Of these, only 6 SAEs reported in 4 patients treated with elafibranor were considered as related to treatment. Nineteen patients discontinued the study for safety reason with no imbalance between groups (6 in the placebo arm, 6 in the elafibranor 80 mg arm, and 7 in the elafibranor 120 mg arm).

1.6. CONCLUSION

Clinical data confirmed the beneficial effect of elafibranor in NASH patients, with efficacy on histology associated with improvement on insulin resistance, and with relevant reductions in markers of liver injury such as GGT and ALT, and in inflammatory markers. It demonstrated also improvement in lipid profile

resulting in a beneficial balance between pro and anti-atherogenic markers. Moreover, it highlighted the good safety profile of elafibranor, since no major safety concerns were raised during these studies.

For additional information see Investigator's Brochure.

1.7. RATIONALE FOR STUDY POPULATION

Given the natural fluctuation of the disease for patients with mild NASH (NAS score of 3), phase IIb study results have clearly highlighted that only NASH patients with moderate to severe disease (NAS score≥4) should be treated.

Regarding fibrosis, available data from meta-analyses demonstrate that NASH patients are at greatest risk of progression to advanced fibrosis, cirrhosis, and liver outcomes. Patients with NASH develop progressive fibrosis in 25% to 50% of individuals over 4-6 years, while 15% to 25% of individuals with NASH can progress to cirrhosis.[20] In another study, with a mean follow-up of 13 years, 13.3% of NASH patients with mild to moderate fibrosis (stage 1-2) and 50% of patients with fibrosis stage 3 at inclusion developed cirrhosis.[21]

Considering these data, it is reasonable to include NASH patients with any stage of fibrosis (stage 1 to 3) in the Phase III program, from both safety and prospect for benefit standpoints. However, since in patients with NASH and advanced fibrosis (F2-F3) the probability of developing cirrhosis is much higher than in patients with early fibrosis (F1), the population evaluated for the long-term outcome needs to be based on the advanced fibrosis patients in order to enhance the chances of demonstrating a benefit within a reasonable timeframe.

Accordingly, the target population for the analysis of surrogate endpoint and liver outcomes will be NASH patients with advanced fibrosis (F2-F3). The enrollment of patients with advanced fibrosis for the evaluation of long-term outcomes including progression to cirrhosis should ensure that an expected number of events, calculated based on progression rate for each fibrosis stage, are obtained. Based on the literature,[21,22,23,24,25] in patients with NASH and advanced fibrosis (F2-F3) this progression rate can be estimated at 8% per year for fibrosis stage 3 and 6% per year for fibrosis stage 2, thus an average of 7% for advanced fibrosis.

As a conservative approach, no supplementary percentage was added to the estimated progression rate to histological cirrhosis (7%) for all the other events of the composite endpoint not linked to cirrhosis. Generally, liver decompensation events occur only when cirrhosis is present and the progression rate to the other events is expected to be very low.

A limited number of NASH patients with fibrosis stage 1 and associated comorbidities known to be at risk of fast disease progression will be included in the study as an exploratory group.

Enrollment of female patients will be capped at 40% in each group for this study to mirror the higher prevalence of NASH in males compared to females.[26]

1.8. JUSTIFICATION OF THE SELECTED DOSE

The results obtained in the Phase IIb study evaluating the resolution of NASH clearly demonstrated the superiority of the elafibranor dose of 120 mg over 80 mg on the histological endpoint, regardless of the population selected (Intent-To-Treat [ITT] or Full Analysis Set) or the subgroup tested, indicating that the dose to be used for the Phase III trial should be 120 mg.

To support this assumption, a dose-response modeling was performed based on data obtained in the Phase I clinical program with 14-day repeated dose studies ranging from 5 mg to 360 mg daily dose. In this model, the studied response was the change at endpoint versus baseline in biochemical parameters known to be associated in a dose-dependent manner with elafibranor exposure, such as liver enzymes (ALT, GGT, alkaline phosphatase), plasma lipids (triglycerides, LDL-C, HDL-C) or serum creatinine. Based on this modeling, the optimum dose was consistently assessed as a value of 118 mg. Therefore, given its good safety profile and evidence of efficacy, both supported by the dose-response modeling, 120 mg elafibranor appears to be the most appropriate dose for the upcoming Phase III trial.

1.9. RATIONALE FOR EFFICACY ENDPOINT

1.9.1. Primary endpoint for application under conditional approval

Steatohepatitis is indirectly associated with reduced hepatic survival in NAFLD.[21,27] It drives fibrogenesis, a slow process of hepatic scar formation that can result in cirrhosis and its deadly complications such as liver failure, portal hypertension, and hepatocellular carcinoma. Consequently, clearance of steatohepatitis,[28] i.e., reversal to a normal liver or to steatosis without steatohepatitis – a condition not associated with increased hepatic morbidity or mortality – is expected to improve hepatic prognosis. Natural history studies are now available showing that patients with steatohepatitis but not those with steatosis only (i.e., nonNASH NAFLD) are the ones that progress to cirrhosis and liver-related outcomes. This forms the basis for "resolution of NASH" as a desirable outcome of therapy in the short-term; a concept widely embraced by the academic community and expressed in several scientific society endorsed position papers.[29,30] Based on the recently published recommendations from this workshop,[30] resolution of NASH with no worsening of fibrosis may be an acceptable surrogate endpoint suitable for a Phase III enrolling patients with NASH and fibrosis. Based on recent data that have shown that fibrosis stage of 2 or more is related to liver-related mortality,[22] the "no worsening of fibrosis" should be no progression of one stage in fibrosis.

1.9.2. Primary endpoint for clinical outcome (postapproval confirmation)

The primary endpoint of the Long-term Treatment Period (LTTP) of the study is to evaluate the effect of elafibranor on the progression to cirrhosis, all-cause mortality, and liver-related clinical outcomes as measured by the onset of any of the listed adjudicated events (clinical outcomes composite endpoint).

Primary endpoint events include overall mortality, progression to cirrhosis, and the full list of portal hypertension/cirrhosis related events (liver transplantation, model end stage liver disease (MELD) score ≥15, hepatocellular carcinoma (HCC), and hospitalization due to occurrence of hepatic encephalopathy, variceal bleeding, spontaneous bacterial peritonitis, uncontrolled ascites, hepatorenal syndrome, hepatopulmonary syndrome, and chronic gastrointestinal blood loss due to portal hypertensive gastropathy [provided that these lead to hospitalization or transfusion]).

Singh et al. recently provided a thorough meta-analysis of paired biopsy studies to obtain the most accurate estimate of the fibrosis progression rate in a large cohort of patients with NAFLD.[25] Over 2145.5 person-years of follow-up evaluation, 33.6% had fibrosis progression, 43.1% had stable fibrosis, and 22.3% had an improvement in fibrosis stage. Overall, the annual fibrosis progression rate in a population of patients with NAFLD who had stage 0 fibrosis at baseline was 0.07 stage/year compared to 0.14 stage/year in a population of patients with NASH. In another study of 108 patients, no significant difference in the proportion exhibiting fibrosis progression was found between those with NAFLD or NASH.[31] In the whole cohort, the mean annual rate of fibrosis progression was 0.08 stage/year.

Based on the literature, in patients with NASH and advanced fibrosis (F2-F3), the probability of developing cirrhosis can be estimated at 8% per year for fibrosis F3 and 6% per year for fibrosis F2.[21,22,23,24,25]

In conclusion, the difference in progression to cirrhosis, other liver-related events, and total deaths between treatment and control groups can be considered as a potential clinically meaningful outcome measure for clinical trials. This long-term outcome including progression to cirrhosis is considered acceptable,[30] and required in a postapproval study for treatments approved under conditional approval.

1.10. RATIONALE FOR STUDY DURATION

In accordance with the AASLD and EASL recommendations, 72-weeks of treatment have been defined for the first stage of the study in order to demonstrate the efficacy of elafibranor on resolution of NASH without worsening of fibrosis.

The estimated duration of the LTTP is based on a 7% probability of patients with NASH and moderate and advanced fibrosis (F2-F3) developing cirrhosis or other liver-related events as determined from recently published data [21,22,23,24,25] and the available data of the mortality risk in this patient population.[32,33]

1.11. RATIONALE FOR SAFETY MONITORING

The safety of use of the dose of 120 mg/d of elafibranor during the proposed trial is supported by the chronic toxicity studies and previous Phase I and Phase II trials. Indeed, the toxicology package of elafibranor does not reveal any major safety concern, based on the conclusion that elafibranor-induced liver toxicity in rodents is not relevant to nonprimates (no evidence of liver toxicity in monkeys after 1 year but improvement of liver function markers) and humans (consistent improvement of liver function markers

in all Phase II trials). These toxicology results and conclusions are on-line with the extensive literature on the liver effects of PPAR agonists.

An independent DSMB will be established in order to review the progress of the study and to perform a safety data review (as defined by the DSMB Charter) on a regular basis during the trial to protect patient welfare and preserve study integrity.

Knowing the risks associated with NASH and disease progression, specific attention will be paid to potential hepatotoxicity, liver-related and cardiovascular events.

Given the known effect of elafibranor on serum creatinine increase, special attention will be paid to all the renal safety markers (plasmatic or urinary parameters), including but not limited to albumin-creatinine ratio, cystatin C, neutrophil gelatinase-associated lipocalin (N-Gal), N acetyl β D-glucosaminidase β-NAG, kidney injury molecule-1 (KIM-1). Serum creatinine, modification of diet in renal disease (MDRD) derived estimated glomerular filtration rate (eGFR), and the results of urinalysis (dipstick) will be reported at each visit, as well as blood urea nitrogen. The other markers (plasmatic or urinary) will be assayed in batch and will be reviewed on an ongoing basis through regular safety reviews by the DSMB which includes a nephrologist.

Assays of many other markers are scheduled in order to monitor liver function markers, cardiac safety markers, and to follow up the cardiovascular profile which is known to be at risk in NASH patients.

For cardiac safety, troponin-T and NT-ProBNP will be followed and reviewed on a regular basis by the DSMB. In addition, electrocardiogram (ECG) and blood pressure (BP) will be routinely monitored throughout the study.

Liver function will be monitored throughout the study, by assessment of liver enzymes, bilirubin (total and conjugated), alkaline phosphatase, and international normalized ratio (INR) reported at each visit.

In addition, even if no safety concern has been revealed in the previous clinical program, all the biological parameters that are known to be affected by PPAR agonists will remain monitored in the Phase III trials, such as hematological parameters, adiponectin, or homocysteine.

During the LTTP, patients will be monitored by clinical and biological assessment. A FibroScan® measurement and noninvasive markers assessment will be performed every 24 weeks, and if cirrhosis is suspected, a confirmation by liver biopsy will be performed.

For additional information see Investigator's Brochure.

2. TRIAL OBJECTIVES

2.1. PRIMARY OBJECTIVES

2.1.1. Surrogate endpoint analysis

To evaluate the efficacy of elafibranor 120 mg QD for 72 weeks versus placebo on resolution of NASH without worsening of fibrosis.

- Resolution of NASH is defined as the disappearance of ballooning and disappearance or persistence of minimal lobular inflammation (grade 0 or 1) with an overall pattern of injury not qualifying for steatohepatitis.
- Worsening of fibrosis is evaluated using the NASH Clinical Research Network (CRN) fibrosis staging system and defined as progression of at least 1 stage.

2.1.2. Long-term endpoint

To evaluate the efficacy of elafibranor 120 mg QD versus placebo on clinical outcomes described as a composite endpoint composed of death due to any cause, liver cirrhosis, and the full list of portal hypertension/cirrhosis related events:

- Liver transplantation
- MELD score ≥15
- HCC
- the onset of:
    - variceal bleed
    - hepatic encephalopathy
    - spontaneous bacterial peritonitis
    - ascites
    - hepatorenal syndrome
    - hepatopulmonary syndrome
    - chronic gastrointestinal blood loss due to portal hypertensive gastropathy (provided that these lead to hospitalization or transfusion).

2.2. KEY SECONDARY OBJECTIVE – AT SURROGATE ENDPOINT ANALYSIS

To assess histological changes after 72 weeks of treatment, at the time of surrogate endpoint analysis, on the following endpoint:

- Percentage of patients with improvement of fibrosis of at least 1 stage according to NASH CRN scoring.

2.3. OTHER SECONDARY OBJECTIVES

- To assess histological changes after 72 weeks of treatment and follow-up biopsy on the following endpoints:
    - percentage of patients with resolution of NASH without worsening of fibrosis (follow-up biopsy)
    - percentage of patients with improvement of fibrosis of at least 1 stage according to NASH CRN scoring
    - percentage of patients with at least 1 point improvement in histological scores (NASH CRN scoring: total NAS, steatosis, hepatic ballooning, lobular inflammation), fibrosis (NAFLD Ishak scoring system), or portal inflammation
    - percentage of patients with improvement of NAS of at least 2 points
    - percentage of patients with at least a 1 point improvement in steatosis-activity-fibrosis (SAF) activity score
    - mean changes in NAS, steatosis, hepatic ballooning, lobular inflammation, portal inflammation, SAF activity score
    - changes in area of fibrosis by morphometry
    - mean changes in fibrosis using NASH CRN and NAFLD Ishak scoring.
- To assess the following endpoints at Week 72 and at the end of the LTTP:
    - changes in liver enzymes and liver markers
    - changes in noninvasive markers of fibrosis and steatosis
    - changes in lipid parameters
    - variation in body weight
    - changes in insulin resistance and glucose homeostasis markers
    - changes in inflammatory markers
    - changes in cardiovascular risk profile as assessed by Framingham scores
    - changes in quality of life (36-Item Short-Form Health Survey [SF-36]) questionnaire).
- To assess the onset to:
    - liver cirrhosis
    - death of any cause
    - any portal hypertension or cirrhosis related events
    - cardiovascular events
    - liver-related death events

2.4. EXPLORATORY OBJECTIVES

- To constitute a biobank for discovery and validation of biomarkers in NASH.

2.5. EXPLORATORY OBJECTIVES FOR F1 GROUP

- To explore the following endpoints in F1 patients in the exploratory group at Week 72 and at the end of the LTTP:
    - resolution of NASH without worsening of fibrosis
    - percentage of patients with at least 1 point reduction in NASH CRN fibrosis score and NAFLD Ishak score
    - percentage of patients with at least 1 point improvement in NAS, steatosis, ballooning, lobular inflammation, or portal inflammation
    - percentage of patients with improvement of NAS of at least 2 points
    - percentage of patients with at least a 1 point improvement in SAF activity score
    - mean changes in NAS, fibrosis (using NASH CRN or NAFLD Ishak scoring system), steatosis, hepatic ballooning, lobular inflammation, portal inflammation, and SAF activity score.
    - changes in area of fibrosis by morphometry.
- To explore the following endpoints in F1 patients at Week 72 and after the LTTP:
    - composite endpoint as described in Section 2.1.2.
    - cardiovascular events
    - changes in liver enzymes and liver markers
    - changes in noninvasive markers of fibrosis and steatosis
    - changes in lipid parameters
    - variation in body weight
    - changes in insulin resistance and glucose homeostasis markers
    - changes in inflammatory markers
    - changes in cardiovascular risk profile as assessed by Framingham scores
    - changes in quality of life (SF-36 questionnaire)
- To assess the tolerability and safety.

2.6. SAFETY SECONDARY OBJECTIVES

To assess the tolerability and safety of once a day administration of oral doses of elafibranor 120 mg:

- SAE, AE, physical examination, vital signs, medical history, ECG
- hematological parameters
- liver markers
- renal biomarkers (including urinalysis)
- cardiac biomarkers
- metabolic parameters
- other biochemical safety markers.

3. TRIAL DESIGN

This is a Phase III, randomized, double-blind, parallel groups, placebo-controlled study, evaluating the efficacy and safety of elafibranor 120 mg QD versus placebo in an adult NASH population with fibrosis.

The first double-blind 72-week Treatment Period will assess the efficacy and safety of elafibranor on the resolution of NASH without worsening of fibrosis at the surrogate endpoint efficacy analysis, followed by a LTTP to assess efficacy on progression to cirrhosis, all-cause mortality, and liver-related clinical outcomes as measured by the onset of any of the listed adjudicated events (see Section 2.1.2). The study will terminate upon the 456th patient (excluding exploratory F1 group [see below]) experiencing an event listed in the composite endpoint for long term efficacy evaluation.

It is planned to randomize patients to either active or placebo treatment in a 2:1 ratio, stratified by type 2 diabetes, gender (with a capping of women to 40%), and fibrosis stage. Additional patients with fibrosis stage 1 (10% of sample size calculated for the F2 and F3 patients) and high risk for progression of NASH will also be enrolled for exploratory purposes.

3.1. NUMBER OF PATIENTS

It is planned to randomize 2022 F2/F3 patients to either active (1348 patients) or placebo (674 patients) treatment in a 2:1 ratio. Up to 202 additional patients (a maximum level of 10% of the F2/F3 enrolled patients) with fibrosis stage of 1 and high risk for progression of NASH (NAS ≥5, F1 patients with at least 2 of the following conditions: persistent elevated (absence of normal ALT within the past year, obesity defined by a body mass index (BMI) ≥30, metabolic syndrome [National Cholesterol Education Program's Adult Treatment Panel III {NCEP ATP III definition}], type 2 diabetes, or HOMA-IR >6) will also be enrolled, and followed as an exploratory group. The F1 patients will not be included in the primary surrogate endpoint and final analysis or in the sample size calculation (detailed in Section 9.7). As such a total of 2224 patients will be enrolled, including the exploratory F1 group.

3.2. METHOD OF ASSIGNING PATIENT TO TREATMENT GROUP

Patients who satisfy all eligibility criteria will be randomly allocated to one of the following groups in a 2:1 ratio:

- Elafibranor 120 mg
- Placebo.

Randomization to treatment will be stratified to ensure balance of treatment allocation by the following 3 factors:

- Type 2 diabetes (yes, no)

- Gender (male, female) (with a capping of women to 40%)
- Fibrosis stage (F1, F2, F3) (capped to 202 F1 patients).

Treatment assignments will be made using an interactive voice/web response system (IXRS).

3.3. DOSE ADJUSTMENT CRITERIA

Not applicable. Patients will be randomized to a fixed dose with no allowance for dose adjustment.

3.4. DURATION OF STUDY PARTICIPATION

The estimated duration of the study will be approximately 72 months, based on 456 patients experiencing an event described in Section 2.1.2 at an assumed annual rate event of 7%. However, this may be redefined according to the actual occurrence of events (described in Section 2.1.2) during the confirmatory part of the study (LTTP).

3.5. STUDY PERIODS

The study will comprise 3 periods. The Screening Period (-12 to -1 weeks) will precede a 72-week double-blind First Treatment Period and a LTTP up to the occurrence of a prespecified number of events.

Study procedures are summarized in Table 1, Table 2, and Figure 1.

Schedule:

- Week -12 to Week -1 prior to Randomization: Screening Period (screening visits SV1 to SPV).
- Week 0 to Week 72: First Treatment Period with Elafibranor or placebo for 72 weeks (visits V1 to V7).
- Week 72 to end of study (EOS): LTTP with elafibranor or placebo until 456 patients experience an event listed in Section 2.1.2 (visits V8 to Vn).

3.6. SCREENING PERIOD (WEEK -12 TO WEEK -1)

3.6.1. Screening visits SV1 and SV2

The following screening procedures will be performed for all potential patients at SV1 conducted during the screening period and prior to randomization:

- Signature of informed consent witnessed by the Investigator or designated person. **Note**: The signature of the informed consent may also be performed before SV1.
- Patient number allocation via IXRS.
- Check medical history/demographics.
- Check inclusion/exclusion criteria (described in Section 4).
- Physical examination (described in Section 6.2.1).

- Adequate diet recommendations (described in Section 5.1.1 and APPENDIX II: Adequate diet and lifestyle recommendations), alcohol restrictions (described in Section 5.1.2), and tobacco habits.
- Record vital signs (described in Section 6.2.3).
- Record height, weight, and waist circumference.
- Check concomitant/prior medication (within 6 months prior to Screening) (described in Section 7.12 and APPENDIX III: Permitted/non-permitted medication)
- Check if a liver biopsy with confirmed NASH and fibrosis is available, and, if so send sample for central confirmation of NASH diagnosis (described in Section 6.1.1.2). This historical diagnostic biopsy should be obtained within 6 months prior to the Screening Visit.
- Check AEs from time of Informed Consent Form (ICF) signature (described in Section 6 and Section 8).

The Screening biological assessment (SB1 will be scheduled at SV1).

If no diagnostic liver biopsy (within 6 months of SV1) is available, it is recommended to schedule an additional SV2 visit at least Week -4 prior to the planned Randomization V1, in order to obtain the results in time.

The following biological assessments (detailed in Table 2) will be performed at SB1:

- Blood samples (described in Table 2).
- Whole blood, plasma & serum bank samples (only if additional genetic and biomarker ICF signed).
- Urinalysis dipstick.
- Urinary pregnancy test (for women of childbearing potential only [WOCBP]).

If no historical values of AST, ALT, total bilirubin and INR meeting the requirements of within 8 weeks to 6 months of randomization visit are available, then SV1 and V1 must be scheduled at least 8 weeks apart in order to have 2 consecutive values for DILI adjudication.

In case of known cured hepatitis C virus (HCV) infection, HCV RNA testing can be done at SV1 without waiting for HCV Ab results.

If needed, a retesting of abnormal HbA1c, or creatine phosphokinase (CPK) results or additional testing of HCV RNA, may be performed during the screening window to determine the eligibility for the study as described in exclusion criteria 5, 12, 30, and 31 (see Section 4.2 and Section 3.11).

At visit SV1, preliminary entrance criteria will be reviewed. Potentially eligible patients will be asked if they agree to participate in the study and sign the ICF. Each patient who has signed the ICF will be allocated a patient number composed of 9 digits which is generated by the IXRS.

- First 3 digits corresponding to the ISO numeric country code (this number will be predefined),
- Next 3 digits corresponding to the site number (this number will be predefined),

- Last 3 digits corresponding to the numerical order of the patient entry at the study site.

A specific IXRS procedure manual will be provided to the Investigator.

3.6.2. Screening Visit SV2 (liver biopsy if required, Week -12 to recommended Week -4):

If no diagnostic liver biopsy within 6 months of SV1 is available, it is recommended to schedule an additional SV2 visit at least Week -4 for a liver biopsy to be performed (described in Section 6.1.1.1). Blood samples for coagulation (detailed in Table 2) will be taken and tested at a local laboratory prior to the liver biopsy. Liver biopsy samples will be sent for central confirmation of NASH diagnosis (described in Section 6.1.1.2).

During this visit AEs (from the time of signing the ICF) will also be checked (described in Section 6 and Section 8).

3.6.3. Screening Phone Visit SPV (Week -1):

Upon receipt of the NASH diagnosis confirmation and the SB1 or any retesting/additional testing results from the central laboratory, the Investigator should check the eligibility with inclusion/exclusion criteria.

If patient meets all inclusion criteria and none of the exclusion criteria (clinical, histological, and biological ones), the Investigator will inform the patient of his/her inclusion/noninclusion status by a phone call within 1 week prior to the Randomization Visit V1. In case of ineligibility, the patient should be contacted as soon as possible.

3.7. FIRST TREATMENT PERIOD (WEEK 0 TO WEEK 72)

Efficacy of elafibranor versus placebo on resolution of NASH without worsening of fibrosis will be evaluated in this first period treatment of 72 weeks.

The NASH will be evaluated for inclusion by a centrally-read liver biopsy taken within 6 months prior to Screening (if no historical biopsy is available for NASH diagnosis, a liver biopsy will be performed during the Screening Period) with:

- Presence of NASH, with at least a score of 1 in each component of the NAS (steatosis scored 0 to 3, ballooning degeneration scored 0 to 2, and lobular inflammation scored 0 to 3) AND NAS ≥4.
- Fibrosis stage 2 and 3.

A group of patients (n=202, 10% of each group) with F1 fibrosis, NAS ≥5, and concomitant cardiometabolic comorbidities, which are associated with rapid progression of the disease (listed in Section 3.1), will also be enrolled and followed as an exploratory group.

During these first 72 weeks of treatment, visits will be scheduled every 12 weeks. Clinical and biological evaluation will be performed during this First Treatment Period.

At the end of the 72-week treatment period, a biopsy will be performed for all the patients under treatment in order to evaluate the effect of elafibranor on the liver histology.

When 1023 patients (F2-F3) complete Week 72 (or discontinue early from the study), a surrogate endpoint analysis will be performed and potentially filed for initial market approval under Subpart H or conditional approval, (see Section 9.8.1 for details).

During the First Treatment Period the patients will return to the site for visits every 12 weeks (±1 week) from the Randomization Visit (V1); however the maximum time period between visits is to be 96 days due to the study drug supply provided to the patient.

A diagnosis of any event listed in the primary composite endpoint described in Section 1.9.2 will result in the permanent discontinuation of study drug and discontinuation from the study, following an end of study treatment (EOT) Visit as described in Section 3.9 and Section 5.2.2).

3.7.1. Randomization Visit V1 (Week 0):

Eligible patients will return to the site at the Randomization Visit V1 and then every 12 weeks in the First Treatment Period of the study until the first 72 weeks of treatment (V7) (surrogate endpoint analysis). The patient will be contacted at least 1 week before each visit to be reminded of procedures and investigational product (IP) return.

If the patient is eligible, the Investigator will register the patient for randomization in the IXRS, prior to any other study procedures. If the system confirms the randomization, it will provide the Investigator with a treatment number for the patient.

The following will be performed only at V1:

- Check inclusion/exclusion criteria (detailed in Section 4).
- Randomization to one of 2 treatments groups (elafibranor or placebo in 2:1 ratio, detailed in Section 3.2) via the IXRS.

3.7.2. First Treatment Period visits V1 to V7 (Week 0 to Week 72):

The following procedures will be performed at each of the 12-week visits from V1 to V7:

- IXRS registration
- Physical examination (described in Section 6.2.1)
- Record vital signs and weight (described in Section 6.2.1 and Section 6.2.3)

- Confirmation of adequate diet and lifestyle compliance (described in Section 5.1.1 and APPENDIX II: Adequate diet and lifestyle recommendations), alcohol restrictions (described in Section 5.1.2), and tobacco habits
- Check concomitant/prior medication (described in Section 7.12 and APPENDIX III: Permitted/non-permitted medication)
- Quality of life assessment (V1, V3, V5, and V7, only; described in Section 6.2.6)
- Check AEs (all visits) and occurrence of any clinical outcome (from V2 onwards) (described in Section 6 and Section 8)
- Study placebo or drug dispensation (described in Section 7.6)
- Blood samples (described in Table 2)
- Plasma & serum bank samples (only if additional genetic and biomarker ICF signed)
- Urinalysis and urinary dipstick (described in Table 2)
- Urinary pregnancy test (for WOCBP only)
- Provision of home pregnancy test kits (for WOCBP only)
- Record result of home pregnancy tests (to be performed every 4 weeks [see Figure 2]) since previous visit (for WOCBP only, every visit from V1)
- Record waist circumference (V1, V3, V5, and V7, only)
- 12-lead ECG (V1, V4, and V7, only; described in Section 6.2.4)
- FibroScan (V1 and V7 only, described in Section 6.2.5)
- Drug accountability (every visit from V2).

Additional procedures to be performed at V7 are:

- Liver biopsy (described in Section 6.1.1). **Note:** the liver biopsy may be performed at V7 or during a separate visit that occurs within the V7 window of 72 weeks ± 1 week from V1. Liver biopsy samples will be sent for central histological evaluation.
- Blood samples for coagulation taken (platelets count and prothrombin time [PT (INR)]; described in Table 2) and tested at a local laboratory prior to the liver biopsy.

3.8. LONG-TERM TREATMENT PERIOD

The main objective to be evaluated during the LTTP will be the prevention of progression to cirrhosis, death due to any cause, or to portal hypertension/cirrhosis related events (as described in Section 1.9.2).

After the 72-week biopsy, patients will continue in the double-blind LTTP, receiving the same treatment as assigned at V1 (elafibranor 120 mg or placebo). Patients will be monitored by notably measuring the appearance of cirrhosis (based on FibroScan measurement associated with biological and/or clinical assessments and confirmed by biopsy).

At or after the 72-week biopsy, a diagnosis of any event listed in the primary composite endpoint described in Section 1.9.2 will result in the permanent discontinuation of study drug and discontinuation of the study following the EOT Visit (as described in Section 3.9 and Section 5.2.3).

3.8.1. Long-term Treatment Period visits (V8 to Vn)

Patients will return to the site every 24 weeks during the LTTP. The patient will be contacted at least 1 week before each visit to be reminded of procedures and IP return.

The following procedures will be performed at each visit from V8 to Vn:

- IXRS registration
- Physical examination (described in Section 6.2.1)
- Record vital signs and weight (described in Section 6.2.1 and Section 6.2.3)
- Confirmation of adequate diet and lifestyle compliance (described in Section 5.1.1 and APPENDIX II: Adequate diet and lifestyle recommendations), alcohol restrictions (described in Section 5.1.2), and tobacco habits
- Check concomitant/prior medication (described in Section 7.12 and APPENDIX III: Permitted/non-permitted medication)
- Quality of life assessment (V8, V9, V11, and every 48 weeks thereafter Section 6.2.6)
- Check AEs and occurrence of any clinical outcome (described in Section 6 and Section 8)
- Study placebo or drug dispensation (described in Section 7.6)
- Blood samples (described in Table 2)
- Plasma & serum bank samples (only if additional genetic and biomarker ICF informed consent signed)
- Urinalysis and urinary dipstick (described in Table 2)
- Urinary pregnancy test (for WOCBP only)
- Provision of home pregnancy test kits (for WOCBP only)
- Record result of home pregnancy tests (to be performed every 4 weeks [see Figure 2]) since previous visit (for WOCBP only, every visit from V1)
- Record waist circumference
- 12-lead ECG (every 48 weeks from V9; described in Section 6.2.4)
- FibroScan (described in Section 6.2.5)
- Drug accountability
- Liver biopsy (at approximately 4 years [V13], and in case of suspected liver cirrhosis, described in Section 6.1.1). Liver biopsy samples will be sent for central histological evaluation
- Blood samples for coagulation taken (platelets count and PT [INR]; described in Table 2) and tested at a local laboratory prior to the liver biopsy.

3.8.2. Long-term Treatment Period phone visits (PV1 to PVn)

Phone visits will be scheduled every 24 weeks starting 12 weeks after Visit 7 for data collection on diet and lifestyle, concomitant medications, clinical outcomes, safety, home pregnancy test results, and IP compliance control. If any information during this phone contact requires a visit, the Investigator may decide to perform an unscheduled visit (described in Section 3.11.2). IXRS registration will be performed for each phone visit.

3.9. END OF STUDY TREATMENT VISIT

At the EOS (upon occurrence of the expected number of events), all patients will be asked to stop treatment and undergo an EOT Visit 30 days after the final administration of study drug.

All patients who permanently discontinue their study medication will undergo an EOT Visit 30 days after the final administration of study drug. Patients who permanently discontinue study drug for any reason other than an event listed in the primary composite endpoint for long-term efficacy described in Section 1.9.2 will remain, upon agreement, in the study after the EOT Visit and be followed up to evaluate efficacy outcomes and safety through phone call visits every 24 weeks as described in Section 3.10 and Section 5.2.

If a patient discontinues from the study, every attempt should be made to have the patient return to the site and complete the EOT Visit 30 days after the final administration of study drug. For details of the EOT Visit see Table 1, Table 2, Figure 1, and Figure 2.

The patient will be contacted at least 1 week before the visit to be reminded of procedures and IP return (if required). The following procedures will be performed at the EOT Visit:

- IXRS registration
- Physical examination (described in Section 6.2.1)
- Record vital signs and weight (described in Section 6.2.1 and Section 6.2.3)
- Confirmation of adequate diet and lifestyle compliance (described in Section 5.1.1 and APPENDIX II: Adequate diet and lifestyle recommendations), alcohol restrictions (described in Section 5.1.2), and tobacco habits
- Check concomitant/prior medication (described in Section 7.12 and APPENDIX III: Permitted/non-permitted medication)
- Quality of life assessment (described in Section 6.2.6)
- Check AEs and occurrence of any clinical outcome(described in Section 6 and Section 8)
- Blood samples (described in Table 2)
- Plasma & serum bank samples (only if additional genetic and biomarker ICF informed consent signed)
- Urinalysis and urinary dipstick (described in Table 2),
- Urinary pregnancy test (for WOCBP only)

- Record results of home pregnancy tests (to be performed every 4 weeks [see Figure 2]) since previous visit (for WOCBP only)
- Record waist circumference
- 12-lead ECG (described in Section 6.2.4)
- Drug accountability.

Patients discontinuing study drug or discontinuing the study will be asked to return all used and unused study treatments at the EOT Visit.

3.10. FOLLOW-UP FOR PATIENTS WHO HAVE PERMANENTLY DISCONTINUED STUDY DRUG

Patients who have permanently discontinued study drug due to an event listed in the primary composite endpoint for long-term efficacy described in Section 1.9.2 will be discontinued from the study following the EOT Visit and have no further follow-up.

Patients who have permanently discontinued study drug for any other reason will remain, upon agreement, in the study and will be followed up with phone visits every 24 weeks (±2 weeks from EOT Visit) following the EOT Visit to report safety, diagnosis of cirrhosis and occurrence of clinical outcomes (as listed below) including liver and cardiovascular events until EOS or the occurrence of an event listed in the primary composite endpoint for long-term efficacy (described in Section 1.9.2), whichever is sooner.

The following procedures will be performed during the follow-up phone visit for patients who have permanently discontinued study drug:

- IXRS registration.
- Reporting of safety information regarding:
    - any new AEs
    - resolution of previous AEs
    - change in severity of existing AEs
    - occurrence of any cardiovascular events
    - occurrence of diabetes (for patients not previously diagnosed with diabetes)
    - worsening of diabetes (for patients previously diagnosed with diabetes).
- Reporting of any change in diet and life style factors
- Reporting of any change (quantitative or qualitative) in therapies post study drug discontinuation
- Reporting of cirrhosis diagnosis (patient to be asked if they have had any histological confirmation of cirrhosis)
- Reporting of any of the following events (primary composite endpoint for long-term efficacy evaluation):
    - liver transplantation
    - MELD score ≥15
    - HCC

- the onset of:
  - variceal bleed
  - hepatic encephalopathy
  - spontaneous bacterial peritonitis
  - ascites
  - hepatorenal syndrome
  - hepatopulmonary syndrome
  - chronic gastrointestinal blood loss due to portal hypertensive gastropathy (provided that these lead to hospitalization or transfusion).
- death due to any cause.

3.11. OPTIONAL VISITS

3.11.1. Retesting screening visits

Upon receipt of results from biological assessment done at SV1, and in case a retesting or additional testing is needed according to the selection criteria, an additional visit will be scheduled according to the recommended timeframe for retesting.

Permitted retesting or additional testing in case of abnormal value at SV1 are:

- CPK: can be repeated prior to Randomization (V1) within 1 to 2 weeks after initial test.
- HCV RNA testing: in case positive HVC Ab test at SV1 required latest 2 weeks prior to Randomization (V1).
- HbA1c: can be repeated at the latest 2 weeks prior to Randomization (V1).

Any other retest deemed necessary by the Investigator should be discussed with the Study Medical Monitors.

3.11.2. Unscheduled visits

An unscheduled visit is defined as any visit to the study unit outside of the protocol-evaluation timepoints where the patient is seen by study unit personnel, e.g., when follow-up assessments are required for safety reasons or when repeat measurements are required out of the screening period (either to confirm a measurement or in case of errors, measuring device failure, etc).

Unscheduled visits will be needed for patients who may require further follow-up due to safety.

3.12. EXPLORATORY/ANCILLARY SUBSTUDY

Exploratory substudies might be performed during the study in sites that have the corresponding capability. Specific study documents will be prepared and Institutional Review Board (IRB)/ Independent Ethics Committee (IEC) and authority approvals shall be obtained when applicable.

4. PATIENT SELECTION

A patient will be eligible for the study only if all of the following criteria apply:

4.1. INCLUSION CRITERIA

Patients must meet all of the following inclusion criteria to be eligible for enrollment in the trial:

1. Males or females aged from 18 to 75 years inclusive at first Screening Visit.
2. Must provide signed written informed consent and agree to comply with the study protocol.
3. Females participating in this study must be of nonchildbearing potential or using highly efficient contraception for the full duration of the study and for 1 month after the end of treatment, as described below:
    - Cessation of menses for at least 12 months due to ovarian failure,
    - Surgical sterilization such as bilateral oopherectomy, hysterectomy, or medically documented ovarian failure
    - If requested by local IRB regulations and/or National laws, sexual abstinence may be considered adequate (the reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient)
    - Using a highly effective nonhormonal method of contraception (bilateral tubal occlusion, vasectomized partner, or intra-uterine device)
    - Double contraception with barrier AND highly effective hormonal method of contraception (oral, intravaginal, or transdermal combined estrogen and progestogen hormonal contraception associated with inhibition of ovulation; oral, injectable, or implantable progestogen-only hormonal contraception associated with inhibition of ovulation; or intrauterine hormone-releasing system). The hormonal contraception must be started at least 1 month prior to Randomization.
4. Histological confirmation of steatohepatitis on a diagnostic liver biopsy by central reading of the slides (biopsy obtained within 6 months prior to Screening or during the Screening Period) with at least 1 in each component of the NAS (steatosis scored 0-3, ballooning degeneration scored 0-2, and lobular inflammation scored 0-3).
5. NAS ≥4.
6. Fibrosis stage of 1 or greater and below 4, according to the NASH CRN fibrosis staging system.
   For patients with fibrosis stage 1, only patients at high risk of progression will be included meaning with a NAS ≥5 and at least 2 of the following conditions: persistent elevated ALT (absence of normal ALT within the past year), obesity defined by a BMI ≥30, metabolic syndrome (NCEP ATP III definition), type 2 diabetes, or HOMA-IR >6.
7. Patients in whom it is safe and practical to proceed with a liver biopsy, and who agree to have:

- 1 liver biopsy during the Screening Period for diagnostic purpose (if no historical biopsy within 6 months before screening is available)
- 1 liver biopsy after 72-weeks of treatment for assessment of the treatment effects on NASH
- a final liver biopsy after approximately 4 years of treatment (V13), unless a liver biopsy has already been performed within the past year
- 1 liver biopsy performed only in the case of suspicion of cirrhosis (to have a histological confirmation.

8. If a patient is treated with 1 of the following drugs: vitamin E (>400 IU/day), polyunsaturated fatty acids (>2 g/day), or ursodeoxycholic acid; a stable dose from at least 6 months prior to diagnostic liver biopsy is required.
9. For patients with type 2 diabetes, glycemia must be controlled. If glycemia is controlled by antidiabetic drugs, change in anti-diabetic therapy must follow these requirements:
    - no qualitative change 6 months prior to diagnostic liver biopsy up to Randomization (i.e., implementation of a new anti-diabetic therapy) for patients treated with metformin, gliptins, sulfonylureas, sodium/glucose cotransporter (SGLT) 2 inhibitors, glucagon-like peptide (GLP)-1 agonists, or insulin. Dose changes of these medications are allowed in the 6 months prior to diagnostic liver biopsy, except for GLP-1 agonists, which must remain on stable dose in the 6 months prior to diagnostic liver biopsy.
    - no implementation of GLP-1 agonists and SGLT2 inhibitors up to 72 weeks of treatment (V7).

    Initiation of any other antidiabetic drugs is allowed after Randomization based on treating physicians' judgment, except for glitazones which are prohibited 6 months prior to diagnostic liver biopsy until the end of treatment.

4.2. EXCLUSION CRITERIA

Patients who meet any of the following criteria will be excluded from entering the study:

1. Known chronic heart failure (Grade I to IV of New York Heart Association classification).
2. History of efficient bariatric surgery within 5 years prior to Screening, or planned bariatric surgery in the course of the study.
3. Uncontrolled hypertension during the Screening Period despite optimal antihypertensive therapy.
4. Type 1 diabetes patients.
5. Patients with HbA1c >9.0%. If abnormal at the first Screening Visit, the HbA1c measurement can be repeated at the latest 2 weeks prior to Randomization. A repeated abnormal HbA1c (HbA1c >9.0%) leads to exclusion.
6. Patients receiving thiazoledinediones (glitazones [pioglitazone, rosiglitazone]), unless the drug was discontinued at least 6 months before the diagnostic liver biopsy.

7. Patients with a history of clinically significant acute cardiac event within 6 months prior to Screening such as: stroke, transient ischemic attack, or coronary heart disease (angina pectoris, myocardial infarction, revascularization procedures).
8. Weight loss of more than 5% within 6 months prior to Randomization.
9. Compensated and decompensated cirrhosis (clinical and/or histological evidence of cirrhosis). Notably, NASH patients with fibrosis stage = 4 according to the NASH CRN fibrosis staging system are excluded.
10. Current or recent history (<5 years) of significant alcohol consumption. For men, significant consumption is typically defined as higher than 30 g pure alcohol per day. For women, it is typically defined as higher than 20 g pure alcohol per day. See APPENDIX IV: Alcohol comparison table.
11. Pregnant or lactating females or females planning to become pregnant during the study period.
12. Other well documented causes of chronic liver disease according to standard diagnostic procedures including, but not restricted to:
    - Positive hepatitis B surface antigen (HBsAg)
    - Positive HCV RNA, (tested for in case of known cured HCV infection, or positive HCV Ab at Screening)
    - Suspicion of drug-induced liver disease
    - Alcoholic liver disease
    - Autoimmune hepatitis
    - Wilson's disease
    - Primary biliary cirrhosis, primary sclerosing cholangitis
    - Genetic homozygous hemochromatosis
    - Known or suspected HCC
    - History or planned liver transplant, or current MELD score >12.
13. Where applicable, patients not covered by Health Insurance System and/or not in compliance with the recommendations of National Law in force applicable to clinical trials.
14. Patients who cannot be contacted in case of emergency.
15. Known hypersensitivity to the investigation product or any of its formulation excipients.
16. Patients with previous exposure to elafibranor.
17. Patients who are currently participating in, plan to participate in, or have participated in an investigational drug trial or medical device trial containing active substance within 30 days or five half-lives, whichever is longer, prior to Screening.

Concomitant medications (see APPENDIX III: Permitted/non-permitted medication):

18. Fibrates are not permitted from 2 months before Randomization. Patients that used statins, ezetimibe, or nonfibrate lipid lowering drugs before Screening may participate if the dosage has been kept constant for at least 2 months prior to Screening.

19. Currently taking drugs that can induce steatosis/steatohepatitis including, but not restricted to: corticosteroids (parenteral & oral chronic administration only), amiodarone (Cordarone), tamoxifen (Nolvadex), and methotrexate (Rheumatrex, Trexall), which are not permitted 30 days prior to Screening and up to end of treatment.
20. Currently taking any medication that could interfere with study medication absorption, distribution, metabolism, or excretion or could lead to induction or inhibition of microsomal enzymes, e.g., indomethacin, which are not permitted from Randomization until end of treatment.

Associated illnesses or conditions:

21. Any medical conditions that may diminish life expectancy to less than 2 years including known cancers.
22. Evidence of any other unstable or, untreated clinically significant immunological, endocrine, hematological, gastrointestinal, neurological, neoplastic, or psychiatric disease
23. Mental instability or incompetence, such that the validity of informed consent or ability to be compliant with the study is uncertain.

In addition to the above criteria, patient should not present any of the following biological exclusion criteria:

24. Positive anti-human immunodeficiency virus (HIV) antibody.
25. AST and/or ALT >10 x upper limit of normal (ULN).
26. Conjugated bilirubin >1.50 mg/dL due to altered hepatic function. Note: Gilbert Disease patients are allowed into the study.
27. INR >1.40 due to altered hepatic function.
28. Platelet count <100,000/mm3 due to portal hypertension.
29. Serum creatinine levels >1.53 mg/dL in males and >1.24 mg/dL in females.
30. Significant renal disease, including nephritic syndrome, chronic kidney disease (defined as patients with markers of kidney damage or eGFR of less than 60 ml/min/1.73 m2).
31. Unexplained serum CPK >3 x the ULN. In case of explained elevated CPK >3 x the ULN, the measurement can be repeated prior to Randomization. In this case, retest should be performed within 1 to 2 weeks after initial test. A CPK retest >3 x ULN leads to exclusion.

5. TRIAL PROCEDURES

The procedures performed at each visit are summarized in the study schedules (see Table 1, Table 2, Figure 1, and Figure 2) and in Section 3.

The Investigator will be asked, whenever possible, to schedule patient visits at the same time of day for each patient. A patient may be seen at any time for reasons of safety.

During each visit, lifestyle and study recommendations will be repeated, vital signs will be measured, and the patient will be queried in the form of an open question regarding new or continuing events.

Procedures for premature discontinuation after SV1 are described in Section 5.2.

5.1. LIFESTYLE RECOMMENDATIONS AND STUDY RECOMMENDATIONS

5.1.1. Standard diet and exercise recommendations

Standard diet and exercise recommendations given by the Investigator during SV1 will be given at the beginning of each patient's participation and will be maintained throughout the study. These recommendations will be based on Therapeutic Lifestyle Change (TLC) counseling (or local equivalent) according to NCEP ATP III guidelines. The essential components of TLC and the macronutrient recommendations for the TLC diet are detailed in APPENDIX II: Adequate diet and lifestyle recommendations.

Assessment of dietary and lifestyle compliance will occur at each visit by asking the patient 2 questions to confirm if they have remained compliant to the diet and lifestyle recommendations. A yes/no response will be recorded in the electronic care report form (eCRF).

5.1.2. Dietary, fluid, and lifestyle restrictions

The following restrictions should be applied to patients in this trial from SV1 through to the end of the study:

- Patients will be required to fast (no food or drink other than water) for at least 12 hours prior to all blood sampling. As such, patients should not consume any breakfast or take any medication (including study medication) in the morning prior the blood sampling. In case the patients do not fast before a visit, a new appointment will be scheduled within 7 days.
- On each study visit day, study treatment will be taken under fasting conditions after the blood sampling (which corresponds to the day of the visit).
- During the 48 hours preceding each study visit, patients should not perform strenuous exercise.
- Patients are to avoid consumption of dietary supplements such as anti-oxidant (including, but not limited to Vitamin A, Vitamin C, provitamin A, selenium, and polyphenol).

- Alcohol consumption should be limited during the study duration and registered in the eCRF. Alcohol consumption of more than 20 g per day for women and 30 g per day for men is considered abusive (see APPENDIX IV: Alcohol comparison table). A standard drink is equal to 14.0 grams (0.6 ounces) of pure alcohol. Generally, this amount of pure alcohol is found in:
    - 12-ounces/350 ml of beer (5% alcohol content)
    - 5-ounces/150 ml of wine (12% alcohol content)
    - 1.5-ounces/50 ml (40% alcohol content) distilled spirits or liquor (e.g., gin, rum, vodka, whiskey).

Concomitant therapy is restricted and any change to treatment or introduction of a new treatment should be discussed with the Investigator before doing so (see Section 7.12 and APPENDIX III: Permitted/non-permitted medication).

5.1.3. Home pregnancy test for women of childbearing potential

Women of childbearing potential are required to perform a pregnancy test every 4 weeks. Home pregnancy test kits will be supplied at each visit to WOCBP and these are to be performed as per the kit instructions every 4 weeks between study visits. Negative results are to be reported at the next scheduled visit or telephone visit (see Table 1 and Figure 2). In the event of a positive result the patient must discontinue study drug immediately and report the result to the Investigator as soon as possible (see Section 8.6.1)

5.1.4. Sun exposure

As a conservative approach patients will be advised to avoid extended ultra-violet light exposure without protection from V1 through to the end of the study (see Section 1.4.4.4).

5.2. PATIENT WITHDRAWAL AND PATIENT TREATMENT DISCONTINUATION RULES

5.2.1. Handling of patient withdrawal

Patients will be informed that they have the right to discontinue the study at any time, for any reason, without affecting future management and treatment.

5.2.2. Permanent discontinuations of study drug

In some instances, it may be necessary for a patient to permanently discontinue study drug. The patient may be discontinued from study drug at any time at the discretion of the Investigator or Sponsor for safety, behavioral, or administrative reasons. In keeping with the ITT analysis, the patient will not be permanently discontinued from the study.

The reason for permanent discontinuation of study drug should be documented in the eCRF and the Medical Monitor informed. If the discontinuation of study drug is due to an AE, the event should be documented in the eCRF.

Some possible reasons that may lead to permanent early study drug discontinuation include:

- Occurrence of any event listed in the composite endpoints for long-term efficacy evaluation (see Section 1.9.2)
- In the opinion of the Investigator, any AE, SAE (described in Section 8), or significant change in a laboratory value that warrants permanent discontinuation of study drug therapy. Investigators are advised to call the Medical Monitor prior to making such a decision
- Occurrence of repeated hypoglycemic episodes without possibility for a down titration of background therapy that may put the patient at risk with continued participation
- Non-permitted concomitant medication (described in Section 7.12 and APPENDIX III: Permitted/non-permitted medication)
- Female patients who are pregnant (see Section 8.6.1) or are breastfeeding or who do not agree to use a reliable method of birth control during the study will be permanently discontinued from study drug
- Non-compliance with the study treatment
- Uncooperative patient
- The patient requests to stop study drug permanently.

Patients permanently discontinued from study drug will be requested to stop taking study drug and attend an EOT Visit 30 days after the last administration of study drug (described in Section 3.9).

If the study drug is discontinued due to the occurrence of any event listed in the composite endpoints for long-term efficacy evaluation (see Section 1.9.2), the patient will also be discontinued from the study with no further follow-up after the EOT Visit.

If the study drug is discontinued due to any reason other than the occurrence of any event listed in the composite endpoints for long-term efficacy evaluation, the patient will undergo, if agreed, telephone visits every 24 weeks (described in Section 3.10) after the EOT Visit until the EOS or the occurrence of any event listed in the primary composite endpoints for long-term efficacy evaluation (see Section 1.9.2), whichever is sooner.

5.2.3. Patient discontinuation from the Study

Patient discontinuation prior to the patient's completion of the study is expected to be low, occurring if the patient withdraws consent, or if enrollment in any other clinical trial involving an investigational product, or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study, occurs.

At the time of discontinuing from the study, the Medical Monitor and IXRS should be contacted, and, if possible, an EOT Visit should be conducted (see Section 3.9). The patient will be permanently discontinued from the study at that time with no further follow-up and the date the patient is withdrawn from the study

and the reason for withdrawal should be appropriately documented in the eCRF. During the study close-out period, survival status will be collected within legal and ethical boundaries for all patients randomized who withdrew participation from the study.

Where possible, patients withdrawn from the study will be followed until resolution of all their SAEs or until the unresolved SAEs are judged by the Investigator to have stabilized.

5.2.4. Patients lost to follow-Up

A patient would be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. Site personnel are expected to make diligent attempts to contact patients who fail to return for a scheduled visit or were otherwise unable to be followed up by the site. Vital status will be collected within legal and ethical boundaries for all patients randomized, including those who did not get study drug. Vital status will be searched in public sources during the study close-out period. If vital status is determined, the patient will not be considered lost to follow-up.

5.2.5. Replacement

No patient replacements are permitted in this study.

5.2.6. Premature discontinuation of the study

Premature termination of this clinical trial may occur because of a Regulatory Authority decision, change in opinion of the IRB/IEC, drug safety problems, DSMB recommendations, or at the discretion of the Sponsor. In addition, the Sponsor retains the right to discontinue development of the study treatment at any time.

The Sponsor reserves the right to discontinue the trial prior to inclusion of the intended number of patients, but intends only to exercise this right for valid scientific or administrative reasons. After such a decision, the Investigator must contact all participating patients within a reasonable period of time. As directed by the Sponsor, all trial materials must be collected and all eCRFs completed to the greatest extent possible.

Furthermore, the Investigator can decide to prematurely discontinue the study. In that event, the Investigator must notify the Sponsor immediately of his/her decision and give the reason in writing. Prompt compliance with this requirement is essential so that the Sponsor may comply with its regulatory obligations.

In all cases, ethics committee (IRB/IEC) and Health Authorities should be informed.

If the Investigator decides to prematurely discontinue the study, all test articles, eCRFs, and related study materials must be returned to the Sponsor.

5.3. PATIENT RESCREENING

Re-screening is allowed in a screen failed patient if there is a change in the situation of the patient which allows him/her to fulfill inclusion/exclusion criteria. This will need sponsor approval. In case of re-screening the patient will need to sign a new informed consent and will be entered as a new patient, with a new patient number.

6. ASSESSMENTS

6.1. EFFICACY AND SAFETY ASSESSMENTS

6.1.1. Histological assessments

A liver biopsy (see Section 6.1.1.1 for recommendations) will be performed:

- At baseline
- After 72 weeks of treatment
- After approximately 4 years of treatment (V13) unless a biopsy has been performed within the previous year.
- In the case cirrhosis is suspected at any interim visit during the LTPP (based on FibroScan and/or clinical and biological assessments)

A Laboratory Manual will be provided to each trial site. The manual will outline the collection process, and shipping requirements for the specific central laboratory.

6.1.1.1. Recommendations related to liver biopsy

Before performing a percutaneous liver biopsy, there must be a clearly defined indication for the biopsy, and the risks to the patient should not outweigh the potential benefits. This will be assessed by the investigator according to local practice.

The patient's platelet count and PT should be checked according to local hospital standards before the date of liver biopsy. Local guidelines and thresholds for hemostatic parameters should be used as they are in everyday clinical practice. Usually a platelet count >80,000/mm^3, a PT >60% or longer by no more than 4 seconds over the control, and a normal bleeding time are acceptable for performing percutaneous liver biopsy in a patient that has stopped taking any antiaggregant therapy for >5 days. If these conditions are not all respected, a safer option would be to perform the liver biopsy by transjugular route, when available.

Sedation is recommended to be given for percutaneous liver biopsy, and should be given with caution in liver disease.

The recommended biopsy procedure to be applied is:

- Needle core biopsy
- Biopsy obtained with a 16 or lower gauge needle
- A tissue core ≥2 cm long (≥10 portal tracts) represents optimal biopsy length
- Preferably obtain biopsy from the right lobe. If left lobe biopsy is used for inclusion, a left lobe biopsy should be used for future biopsies.

Post-biopsy observation: It is recommended that the patient should remain in hospital at least for 6 hours after the procedure.

The biopsies will be sent to the central laboratory and then to a central reader who will read the biopsies to determine the eligibility to the study according the fibrosis stage and consistency with NASH diagnosis. Biopsy slides will be blinded for patient and visit identification prior to central reading.

In case the liver biopsy fragment is too small or of bad quality, thereby precluding adequate reading, other available slides or new slides to be prepared from an available block of tissue may be requested to the site.

6.1.1.2. Liver biopsy reading for NAS and NASH CRN fibrosis score

Histological changes from baseline to Week 72 and any follow-up biopsy will be evaluated. Liver biopsy samples will be sent to the central pathology laboratory (Hôpital Beaujon, 100 Boulevard du Général Leclerc, 92110 Clichy – France) where they will be read and scored. Scores for total NAS, steatosis, ballooning, lobular inflammation, or portal inflammation, as well as fibrosis scores (both by NASH CRN scoring system, and NAFLD Ishak scoring system) and fibrosis area by morphometry will be evaluated.

6.1.2. Biological assessments

All blood samples for efficacy and/or for safety assessment (as described in Table 2) will be returned and centralized by the central laboratory (BARC: Ghent – Belgium, New York – USA, Sydney – Australia, or Johannesburg – South Africa) and specific analyses will be performed by another laboratory (GENFIT-Loos, France).

A laboratory manual will be provided to each trial site.

The manual will outline the collection process and shipping requirements for the specific central laboratory. Blood sampling will be performed by trained personnel at each site. Blood samples will be processed and shipped as outlined in the laboratory manual. Refer to the laboratory manual for exact amounts of blood required for each test.

For all visits, reportable laboratory results (except serology) will be available at sites approximately 24 hours after receipt of samples. Final results will be sent to sites. Laboratory reports should be reviewed, signed, and dated by the Investigator as soon as they are received. The Investigator should comment upon out of range parameters and assess clinical significance.

The option to retest during the study is left to the Investigator's judgment. During Screening, retesting (to be performed at retesting screening visits) is limited to HbA1c, CPK, and HCV RNA, as described Section 3.11. Any other retest deemed necessary by the Investigator should be discussed with the Study Medical Monitors.

In case the lab sampling may not be performed at the scheduled visit, patients should come back to the site within 7 days of the visit for lab sampling.

6.1.2.1. Laboratory assessments

Clinical laboratory evaluations (including hematology, blood chemistry, and urinalysis) will be measured at every visit as described in Table 2.

Hematology and urinalysis (dipstick) will be measured at all visits. Both blood and urine sample will be transported to the central laboratory for testing and analysis. At Screening, the Screening Visit 1 chemistry panel will be measured.

The V1 to Vn total chemistry panel and urine analysis will be measured at all visits from V1 to EOT visits. It is recommended to collect first morning urine samples for urinalysis.

6.1.2.2. Urinary pregnancy tests

Urinary pregnancy tests will be supplied to each site to perform a pregnancy diagnostic at each visit during the study on WOCBP. These tests will also be given to the WOCBP to perform a pregnancy test at home every 4 weeks in between visits (see Section 5.1.3).

6.1.2.3. Serology (SB1)

Screens for a hepatitis panel and HIV antibodies will be performed at SV1:

- HIV ab I/II
- HBsAg
- HCV ab (in case of known cured HCV infection, HCV RNA can be tested directly at SV1; otherwise, HCV RNA should be tested at a Retesting Screening Visit, only in case HCV ab>0 at SV1 [see Section 3.11.1])

6.1.2.4. Other parameters

Liver markers, calculated fibrosis and steatosis index, safety, and inflammatory markers, as well as special glycemic and lipid parameters, will be measured at V1, V3, V5, and V7 during the First Treatment Period, at each visit during LTTP, and at the EOT visit. CHI3L1 will only be tested at V1, V7, and V13 (at the time of the approximate 4 year biopsy).

6.1.3. Constitution of biobank

In order to be able to test other specific parameters which could be of interest regarding the elafibranor development program or regarding diagnosis, prevention, or treatment of NASH or other related diseases, an additional amount of serum & plasma will be kept at each visit (including screening visits) from patients who have given their consent for these additional analyses by signature of the genetic and biomarker ICF.

These samples will be used:

- To discover or validate biomarkers in NASH and related diseases.
- To investigate the role of selected single nucleotide polymorphisms in the response to treatment.

These samples will be destroyed 3 years after study results at the latest.

6.2. OTHER SAFETY ASSESSMENTS AND ONGOING SAFETY MONITORING

6.2.1. Physical examination

A physical examination will be performed and weight measured at each visit (with the exception of the potential SV2). Height will be measured at SV1 only.

The patient's weight will be measured under the same conditions at each visit. Where possible, the scale for weight must be the same for a given patient throughout the visits.

6.2.2. Waist circumference

Waist circumference will be measured at the midpoint between the lateral iliac crest and the lowest rib in cm during expiration. The measuring tape should be snug but not compressing the skin and held parallel to the floor. The measurement is to be made at normal respiration.

6.2.3. Vital signs

Blood pressure (mmHg) and pulse rate (beats per minute) will be measured at each visit (with the exception of the potential SV2 visit) according to the "Recommendations for Blood Pressure Measurement in Humans and Experimental Animals" published in an American Heart Association scientific statement.

6.2.3.1. Important points for clinical blood pressure measurement

- The patient should be seated comfortably with the back supported and the upper arm bare without constrictive clothing. The legs should not be crossed.
- The arm should be supported at heart level, and the bladder of the cuff should encircle at least 80% of the arm circumference.
- When using a mercury sphygmomanometer, the mercury should be deflated at 2 to 3 mm/s, and the first and last audible sounds should be taken as systolic and diastolic pressure. The column should be read to the nearest 2 mmHg.
- Neither the patient nor the observer should talk during the measurement.

Systolic BP and diastolic BP will be measured after 5 minutes rest in the seating position with a standard mercury sphygmomanometer or a validated sphygmomanometer. Where possible, the validated manometer should be the same for a given patient throughout the visits.

6.2.4. Electrocardiogram

A standard 12-lead ECG will be obtained at V1, V4, and V7 in the First Treatment Period, every 48 weeks in the LTTP starting at V9, and at the EOT visit.

Electrocardiograms will be recorded using 12-lead ECG recorders following 10 minutes rest in the supine position. A minimum of 3 cycles will be recorded per lead.

The ECGs will be analyzed by the Investigator. Any potential clinical significance of ECG changes will be determined by the Investigator with relation to the patient's medical history, physical examination, and concomitant medications and recorded in the eCRF.

6.2.5. FibroScan

A FibroScan exam will be performed at V1 and V7 in the First Treatment Period and at each visit in the LTTP under 2 hour fasting conditions. Where possible, FibroScan must be done at the day of visit. Otherwise, it can be performed within 7 days around the visit date.

In case of result ≥14 kPa or of sudden increase from previous measurement, a repeated measurement will be required 4 weeks later (to be performed at an unscheduled visit).

If at baseline, the measurement gives a value ≥14 kPa but without being associated with confirmed histological cirrhosis, a FibroScan measurement will be continued as planned in the protocol but will not be used for the detection of cirrhosis (no repeat test required for patients with baseline≥14 kPa at V1).

6.2.6. Quality of life questionnaire

A standardized and validated questionnaire for quality of life (SF-36) will be completed by patients at V1, V3, V5, and V7 in the First Treatment Period, and V8, V9, V11, and every 48 weeks thereafter in the LTTP until, and including the EOT visit.

6.3. IMPORTANT SPECIFIC BIOLOGICAL CONSIDERATIONS AND PATIENT DISCONTINUATION RULES

6.3.1. Creatine phosphokinase

If at any visit during the treatment periods, a patient experiences diffuse myalgia, muscle tenderness, and/or marked increase in muscle CPK values (≥3 x ULN and ≤5 x ULN), an additional visit and test within 3 to 7 days must be performed. If, during that visit, the patient still experiences diffuse myalgia, muscle tenderness and/or marked increase in muscle CPK values (≥3 x ULN and ≤5 x ULN), myopathy must be considered and the patient must be discontinued from study treatment immediately and followed up as described in Section 5.2.2.

If at any visit during the treatment periods, a patient experiences marked increase in muscle CPK values >5 x ULN, unexplained by strenuous exercise or trauma, the patient must be discontinued from study treatment immediately and followed up as described in Section 5.2.2. In case of exercise and/or trauma, the CPK should be repeated once weekly to verify decrease of CPK, until CPK lowers to ≤5 x ULN.

6.3.2. Liver function monitoring

All liver decompensation events included in the composite efficacy endpoint (Section 1.9.2) will be adjudicated by the Clinical Events Committee (CEC; see Section 6.5), as well as all DILI events (see Section 6.5).

For DILI adjudication, assessment may be performed using as baseline either historical AST, ALT, total bilirubin, and INR results meeting the requirements of within 8 weeks to 6 months of planned randomization visit (V1), or, using lab results from SV1 and V1 that are at least 8 weeks apart.

In all cases, whether baseline AT values are normal or elevated, an increase of AT >10 x ULN will lead to permanent discontinuation of the patient from study drug, and scheduling of EOT visit (Section 3.9).

6.3.2.1. Monitoring of patients with normal baseline aminotransferase values

Liver function monitoring requirements for patients with normal baseline AT values at V1 who at any visit from V2 onwards during the treatment periods exhibit:

- Increase in AT to ≤3 x ULN: no additional action required, schedule next visit as per assessment schedule
- Increase in AT to >3 x ULN but ≤5 x ULN: retest after 48 to 72 hours
  If during the following retest:
  - AT remains >3 x ULN but ≤5 x ULN: continue the drug with close serial monitoring (once a week)
  - AT increases to >5 x ULN: permanently discontinue patient from study drug and schedule EOT Visit (see Section 3.9 and Section 5.2.2).
- Increase in AT >5 x ULN: retest after 48 to 72 hours
  If during the following retest:
  - AT remains >5 x ULN: permanently discontinue patient from study drug and schedule EOT Visit (see Section 3.9 and Section 5.2.2)
  - AT reduces to ≤5 x ULN: continue the drug with close serial monitoring (once a week).
- Increase in AT >3 x ULN AND increase in total bilirubin > 2 ULN: permanently discontinue patient from study drug and schedule EOT Visit (see Section 3.9 and Section 5.2.2).
- Increase in AT >3 x ULN AND increase in INR>1.5: permanently discontinue patient from study drug and schedule EOT Visit (see Section 3.9 and Section 5.2.2).

- Increase in AT >3 x ULN AND fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%): permanently discontinue patient from study drug and schedule EOT Visit (see Section 3.9 and Section 5.2.2).

6.3.2.2. Monitoring of patients with increased baseline aminotransferase values

Liver function monitoring requirements for patients with increased AT baseline values at V1 who at any visit post V1 onwards during the treatment periods exhibit:

- Increase in AT to ≤3 x baseline value: no additional action required, schedule next visit as per assessment schedule
- Increase in AT to >3 x baseline value but ≤10 x ULN: retest after 48 to 72 hours
    - AT remains >3 x baseline value but ≤ 10 x ULN: continue the drug with close serial monitoring (once a week)
    - AT increases > 5 x baseline value or >10 x ULN: permanently discontinue patient from study drug and schedule EOT Visit (see Section 3.9 and Section 5.2.2).
- Increase in AT >3 x baseline value AND increase in total bilirubin > 2 x ULN: permanently discontinue patient from study drug and schedule EOT Visit (see Section 3.9 and Section 5.2.2).
- Increase in AT >3 x baseline value AND increase in INR>1.5: permanently discontinue patient from study drug and schedule EOT Visit (see Section 3.9 and Section 5.2.2).
- Increase in AT >3x baseline value AND fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%): permanently discontinue patient from study drug and schedule EOT Visit (see Section 3.9 and Section 5.2.2).

6.3.3. Threshold for diagnosis of cirrhosis

A FibroScan and serum markers assessments will be performed every 24 weeks at each visit in the LTTP.

In case of FibroScan ≥14 kPa, the examination will be repeated 4 weeks later (at an unscheduled visit). A liver biopsy may be considered in order to confirm the diagnosis of cirrhosis, if the repeat FibroScan value is confirmed ≥14 kPa, and associated with a platelet count <150 000/mm^3 and at least 1 elevated serum marker of fibrosis indicative of cirrhosis (calculated NAFLD fibrosis >0.676 score or reported FIB-4 >2.67). In the case of detection of variceal rupture at endoscopy or of presence of any cirrhosis related event, such as MELD ≥15, hepatic encephalopathy, or ascites, then the liver biopsy will not be required for diagnosis of cirrhosis, but the diagnosed event will have to be adjudicated by the CEC.

If cirrhosis or any event listed in the long-term composite endpoint is diagnosed, the patient will discontinue the study drug and the study and will be followed up as described in Section 5.2.2 and Section 5.2.3.

6.4. SAFETY & EFFICACY DATA REVIEW

An independent DSMB will be established in order to review the progress of the study and to perform a safety data review on a regular basis during the trial to protect patient welfare and preserve study integrity. The DSMB will also review the interim analysis results and provide final recommendations regarding trial termination due to futility and adjustment of the target number of primary events. A detailed description of the interim analysis procedures and decision-making process will be provided in the DSMB Charter.

The DSMB will consist of at least 5 experienced physicians (1 endocrinologist, 1 cardiologist, 1 hepatologist, 1 oncologist, and 1 nephrologist) and 1 statistician, all of whom will be independent of the participants in the study. The DSMB Charter will define the role, responsibilities, rules, and tasks of the DSMB.

6.5. CLINICAL EVENT COMMITTEE

The CEC will conduct adjudication of all disease progression events included in the primary composite efficacy long-term endpoint (Section 1.9.2, except for histological cirrhosis), all DILI events, and all major cardiovascular events as defined in the CEC charter. The CEC assessment and adjudication will occur in a blinded, consistent, and unbiased manner throughout the course of a study to determine whether the endpoints meet the protocol-specified criteria.

The CEC will be comprised of 2 hepatologists, 2 cardiologists, and 1 endocrinologist, all of whom will be independent of the participants in the study.

6.6. GUIDANCE FOR INVESTIGATORS

6.6.1. Summary of safety data

The safety and tolerability of elafibranor were confirmed in Phase I and Phase II studies.

A Phase I program to assess the safety and tolerability, as well as the PK profile, of elafibranor has been conducted through 12 clinical trials, 1 of which is still ongoing. A total of 621 volunteers were randomized in these studies performed in Phase I centers, including 549 healthy lean subjects, 60 overweight or obese subjects, and 12 patients with type 2 diabetes.

A Phase II program was initiated to assess the safety and efficacy profile of elafibranor in patients suffering from cardiometabolic disorders. To date, 5 Phase IIa pilot trials have been completed in which 297 patients were randomized. A Phase IIb trial has been completed, and evaluated the efficacy and safety of elafibranor 80 mg and 120 mg on steatohepatitis in 274 patients with NASH.

Of the 69 SAEs that have been reported cumulatively in the clinical development program, 48 occurred with elafibranor, 13 with placebo, and 8 prior to administration of study medication. For all SAEs, the treatment code has been broken (end of study unblinding).

Of the 48 SAEs that occurred with elafibranor, only 9 were considered as having a reasonable possibility of relationship to elafibranor by the investigators (serious adverse reaction). They consisted of:

- Atrial fibrillation in a patient with history of arterial hypertension and suspected chronic coronary disease treated with elafibranor 80 mg
- Acute cholecystitis and pancreatitis that occurred in a patient on the second day of drug administration of elafibranor 80 mg
- Spontaneous abortion in a pregnant patient treated for 6 months with elafibranor 80 mg
- Ataxia, tremor and fasciculations in a patient treated for 51 weeks with elafibranor 80 mg
- Acute pancreatitis that occurred after 7 weeks of treatment in a patient treated with elafibranor 120 mg.
- Parkinson's disease in a patient treated for 12 months with elafibranor 120 mg, aged 76 years (in the risk group for Parkinson's disease, and with a family history of Parkinson's disease).

For 3 of the cases (atrial fibrillation, acute cholecystitis and pancreatitis, and Parkinson's disease) after later investigations, given the medical history of the patients or the time of occurrence of the event, relationship to elafibranor was judged as "no reasonable possibility" by the Sponsor.

All adverse reactions (adverse events reported by investigators as possibly related or related to study drug) reported in more than 1% of patients treated with elafibranor in clinical studies with repeated doses of at least 80 mg elafibranor per day are summarized in Table 3.

Table 3: Overview of the common nonserious adverse reactions (>1% of patients treated with elafibranor) by system organ class (SOC) reported in completed elafibranor clinical studies with repeated administration of elafibranor (at least 14 days) from 80 mg/day up to 300 mg/day (MTD)

System Organ Class	Adverse Reaction	Severity	Frequency
Gastrointestinal disorders	Nausea	Mild to severe	4.4%
	Diarrhea	Mild to moderate	3.3%
	Vomiting	Mild to moderate	1.6%
General disorders and administration site conditions	Fatigue	Mild to moderate	1.9%
	Asthenia	Mild to moderate	1.1%
Investigations	Hepatic enzymes increased (mainly transaminases)	Mild to severe	1.8%
	Blood creatine phosphokinase increased	Mild to moderate	1.1%
Musculoskeletal and connective tissue disorders	Myalgia	Mild to severe	1.6%
Metabolism & nutrition disorders	Decrease appetite	Mild to severe	1.6%
Renal and urinary disorders	Renal failure/impairment	Mild to moderate	1.2%
Vascular disorders	Hot flush	Mild to moderate	1.2%

Among the non-serious adverse reactions, the most frequent were gastro-intestinal disorders and general disorders. The first ones consisted mostly of nausea, diarrhea, and vomiting. For general disorders, the main symptoms were fatigue or asthenia. These are considered common and expected.

Other non-serious adverse reactions reported in more than 1% of patients concerned changes in biological parameters such as liver enzymes increase (mainly AT), CPK elevation, or increase of creatinine (reported by investigators as renal failure and/or impairment due to the calculation of creatinine clearance by MDRD based on creatinine). Myalgia, decrease of appetite and hot flush were also reported in more than 1% of patients but remain limited.

Regarding specific monitoring, although no signal for increase in CPK has been observed in the clinical trials, given the known effects of PPARα agonists on the increase of CPK enzyme, this parameter is monitored in clinical trials. For this reason, it is recommended that investigators review these lab results in the course of clinical trials.

Other known effects of PPARα agonists include the increase of creatinine, which was observed in our phase IIa and IIb trials, in a range of 5-10%. This increase was reversible at end of treatment. This should also be monitored in clinical trials.

Liver enzymes will also be monitored in clinical trials, with specific attention paid to DILI.

Based on the findings of nonclinical reproductive and developmental toxicity studies performed to date, and in the absence of human pregnancy data, elafibranor may be classed in the "Possible human teratogenicity/fetotoxicity in early pregnancy" risk category according to the Clinical Trial Facilitation Group (CTFG) document Recommendations related to contraception and pregnancy testing in clinical trials (September 2014)[34].

As such, all clinical trials with elafibranor including WOCBP request a negative pregnancy test before Randomization, with effective contraceptive measures throughout the study. It is recommended to maintain the contraception up to 1 month after end of treatment. Pregnancy tests should be repeated as stated in each study protocol. In the absence of a clinical pharmacokinetic interaction study between elafibranor and contraceptive steroids, the exclusive use of hormonal contraceptive methods during clinical trials should be avoided, and they should be accompanied by barrier methods.

6.6.2. Safety data conclusion

Based on the cumulative experience gathered to date, gastro-intestinal disorders such as nausea, diarrhea and vomiting, and asthenia or fatigue are considered common and expected adverse reactions reasonably associated with elafibranor. Most of them are of mild to moderate intensity. As previously, laboratory increases of serum creatinine or CPK should be monitored throughout clinical trials as this has been observed in Phase II trials, and is a known PPARα agonist effect. Elevation of AT will be monitored as well as DILI. In the absence of human pregnancy data, double contraception should be maintained for women

of childbearing potential participating in clinical trials with elafibranor treatment, up to 1 month after end of study treatment.

6.6.3. Benefit/risk assessment

Numerous Phase I and Phase IIa clinical studies have provided data that support the therapeutic potential of elafibranor in metabolic diseases including NASH. Moreover, the Phase IIb trial demonstrated the efficacy of elafibranor at the therapeutic dose of 120 mg on a clinically meaningful primary endpoint, resolution of histological NASH without worsening of fibrosis, in patients with active disease (NAS ≥4). While the trial was short and not designed for antifibrotic endpoints, it nonetheless showed that elafibranor, at 120 mg daily, improved fibrosis indirectly through the resolution of NASH. Importantly, elafibranor 120 mg concomitantly improved the cardiometabolic risk profile of the patients by decreasing plasma triglycerides, total and LDL-cholesterol, increasing HDL-cholesterol, and improving inflammation, insulin resistance, and glucose homeostasis. Together these results position elafibranor as a drug candidate to treat NASH with the objective to block fibrosis evolution and ultimately avoid long term liver outcomes while reducing cardiovascular risk.

Moreover, clinical studies completed to date have not raised any major safety concerns associated with elafibranor treatment, thus providing a favorable efficacy/safety profile for the drug candidate.

Despite this favorable benefit-risk profile, an independent Data Safety Monitoring Board (DSMB) is to be established in order to review the safety of the treatment during the trial in an unblinded manner, to protect patient welfare and preserve study integrity. The safety assessments will be performed on a regular basis, every 6 months after Randomization of the first patient. The DSMB will consist of 5 experienced physicians (1 endocrinologist, 1 cardiologist, 1 hepatologist, 1 oncologist, and 1 nephrologist) and 1 statistician, all independent of the participants in the study.

In addition, throughout the study, patients will benefit from close safety monitoring including assessment of many safety parameters and follow-up of the disease progression, mainly through noninvasive measures including FibroScan.

7. TREATMENTS

7.1. DESCRIPTION OF STUDY MEDICATIONS

Elafibranor (propanoic acid, 2-[2,6-dimethyl-4-[3-[4-(methylthio)phenyl]-3-oxo-1(E)-propenyl] phenoxy]-2-methylpropanoic acid) will be supplied as 120 mg white to off-white round coated tablets with no printed inscription. The tablet contains elafibranor and inactive ingredients [redacted]

Placebo to match elafibranor 120 mg will be provided as a white to off-white round coated tablet with no printed inscription.

For additional information see Investigator's Brochure.

7.2. PACKAGING AND LABELING

7.2.1. Packaging

Elafibranor/placebo:

The primary packaging is composed of opaque polyamide/aluminum/PVC complex and aluminum foil blisters. This has been shown to be a suitable primary packaging for tablets.

Blisters, containing 8 tablets each, will be packed in child proof wallets.

Each childproof wallet will contain 4 blisters. Three wallets will be packaged inside a carton.

7.2.2. Labeling

All labels for study drugs meet all applicable requirements of the US Food and Drug Administration (FDA) and the EU annex 13 of Good Manufacturing Practices: Manufacture of Investigational Medicinal Products (February 2010) and /or other local regulations, as applicable.

Distribution of study drug will be performed according to the Good Distribution Practices.

Product cartons will be labeled with the protocol number, Sponsor's name and address, description of contents, storage conditions, expiry date, dosage instructions, and any other applicable items required by national and regional guidelines/regulations. The label will contain the statements "For clinical trial use only" or other similar/appropriate statements as well as the following instructions "Please return empty packaging and unused products to your doctor at your next visit." Details of carton and wallet labels are detailed in APPENDIX V: Product carton and wallet labeling

.

7.3. DOSAGE AND ADMINISTRATION OF ELAFIBRANOR AND PLACEBO

Patients will be informed to take one tablet per day of elafibranor 120 mg or placebo orally before breakfast with a glass of water each morning.

7.4. METHOD OF ASSIGNING PATIENT TO TREATMENT GROUP

Upon screening of the first patient, the IXRS system will immediately forward the information to the Drug Distribution Center which will be responsible to send one of several blocks of treatment packages (containing 96 tablets to last approximately 3 months) allocated to the site. The pharmacy will acknowledge receipt of the study drug in the IXRS.

An e-mail, confirming that the patient has been screened, will be sent to the Investigator, [redacted] and to the Sponsor.

After having received the liver biopsy results as well as the SV1 laboratory results (SB1) (or when applicable, results of any retesting performed), and if the patient fulfills all criteria to enter the treatment period, the Investigator will register the patient in the IXRS to randomize him/her.

The IXRS will check if the Investigator is authorized to use the system (identification number and access code) and will ask some questions to check the patient eligibility. The IXRS will then allocate the patient to a treatment group (elafibranor 120 mg or placebo) through a patient number (with 9 digits), as described in Section 3.2.

A specific IXRS procedure manual will be provided to the pharmacy.

The randomization list will be generated by the IXRS partner and will be kept in blinding condition to the study participants until the Blind-Review Meeting and the Sponsor authorization to unblind the trial.

7.5. STORAGE CONDITIONS

Elafibranor and placebo should be stored between +15°C and +25°C (59°F and 77°F). Storage conditions are specified on the label.

7.6. DISPENSING OF TREATMENT

Each site will have a resupply strategy within the IXRS to determine the supply of study drugs sent to each site. Initial site shipments will be shipped at a static value defined in the supply strategy. Following randomization of a patient IXRS will project for the amount of study drug required for future visits and ensure the study drug is at site for the visits occurring. The IXRS will continue to project study drug requirements per patient until an event occurs which stops the projections for that patient.

The Investigator will register the patient's visit in the IXRS who will allocate to the patient a treatment package for approximately 3 months (96 tablets) in the First Treatment Period and for approximately 6 months (192 tablets) in the LTTP. An e-mail, confirming the registration, will be sent to the Investigator and to the Sponsor.

The treatment package will include a carton with 3 wallets of 4 blisters for the First Treatment Period and 2 cartons with 3 wallets of 4 blisters in the LTTP.

Each randomized patient will be given, from V1 and at every following visit, the study medication containing the adequate number of wallets to cover the drug administration for the period between visits. The time between visits will be 12 weeks ± 1 week (to a maximum of 96 days) during the First Treatment Period and 24 weeks ± 2 weeks (to a maximum of 192 days) between visits in the LTTP, which correspond to the number of tablets provided to the patient at each visit.

7.7. TREATMENT REPLACEMENT

A specific IXRS procedure manual will be provided to the Investigator and will detail the procedure in case of need of treatment replacement.

7.8. PROCEDURE FOR BLINDING

The Investigator, patient, and study personnel will be blinded to the treatment.

Identification numbers will be assigned to a patient at the Screening Visit. The number will also be reported in the eCRF. Upon completion of the Screening Visit(s), eligible patients will be randomly assigned to active treatment (elafibranor 120 mg) or placebo at the first visit of the First Treatment Period (V1).

7.9. PROCEDURE FOR UNBLINDING

The randomization code may be broken by the Investigator when urgent action is required for the clinical management of the patient. For each patient, the list of treatment numbers allocated to the patient will be stored in the IXRS. The Investigator will be able to unblind any treatment carton that was dispensed to the patient by connecting to the IXRS (**24-hour & 7-day access**) and entering their identification number and access code. A back-up phone Interactive Response Technology (IRT) module will also be available should the site be unable to access the internet. The IXRS will verify the authorization to unblind the entered treatment carton and the screen will then display the treatment group, when completed, a blinded confirmatory e-mail will be sent to the Investigator and the Sponsor.

The reason for unblinding should be clearly and fully documented by the Investigator.

7.10. STUDY DRUG COMPLIANCE

From V2 and at every following visit while the patient is being treated with study drug, the patient will be directed to bring back all used and unused cartons and blisters. Compliance will be checked by the Investigator during those visits and registered in the eCRF.

If treatment is interrupted, whatever the cause, duration and reason of the interruption should be documented.

7.11. TREATMENT ACCOUNTABILITY, RETRIEVAL AND DESTRUCTION.

The Investigator or pharmacist will acknowledge receipt for each study treatment on the day of receipt. A drug accountability record should be maintained by the person responsible for dispensing the trial medication to the patient.

All partially used or unused treatments will be inventoried by the monitor during and at the conclusion of the study.

On Sponsor request, the Drug Distribution Center will organize the retrieval of all treatments (used or unused) and will proceed to their destruction only after the Sponsor provides written authorization.

If the site has an appropriate Standard Operating Procedure (SOP) for drug destruction, the site may destroy used and unused study drugs in accordance with the site SOP and always after the drug accountability has been performed by the monitor.

If drug is destroyed in the site, the Investigator must maintain accurate records for treatment cartons destroyed recording:

- Treatment carton (kit) number (see APPENDIX V: Product carton and wallet labeling
-)
- Quantity destroyed
- Method of destruction
- Person who disposed the drug.

7.12. OTHER MEDICATION

7.12.1. Handling of concomitant medication

In a general manner, patients should be discouraged from starting any new medication without consulting the Investigator unless the new medication is required for emergency purpose. In the same way, any qualitative or quantitative change in concomitant therapy should be avoided, when possible (see table II, APPENDIX III: Permitted/non-permitted medication). In the event that it becomes necessary during the study, this should be recorded by the Investigator in the eCRF (including concomitant medications taken

within 6 months prior to Screening) and information should be communicated to the Medical Monitor in order to evaluate the risk of DDIs. This includes drugs used on a chronic as well as on an "as needed" basis.

7.12.2. Non-permitted medication (see Table I, APPENDIX III: Permitted/non-permitted medication)

The following medications are not allowed within the timeframe given in APPENDIX III: Permitted/non-permitted medication):

- Thiazoledinediones (glitazones [pioglitazone & rosiglitazone])
- Fibrates
- Corticosteroids (parenteral & oral chronic administration only)
- Amiodarone
- Tamoxifen
- Methotrexate
- Indomethacin.

The following medications are not allowed to be initiated prior to diagnostic liver biopsy and up to 72 weeks of treatment (see APPENDIX III: Permitted/non-permitted medication):

- GLP-1 agonist
- SGLT2 inhibitors.

If it is identified that these non-permitted drugs have been administered to a patient within the excluded timeframes, the site will discuss the continuation of the patient with the Medical Monitors of the study.

7.12.3. Permitted medication under condition (see Table II, APPENDIX III: Permitted/non-permitted medication)

The following medications are permitted under the condition of steady dosage prior to Screening (dose changes are allowed after Randomization if judged necessary by the physician):

- Statins, ezetimibe, and other nonfibrate lipid lowering medications, provided the dosage is kept stable for at least 2 months prior to Screening.

The following medications are permitted under the condition of stable dose from at least 6 months prior to diagnostic liver biopsy (dose changes should be avoided up to EOT):

- Vitamin E >400 IU/day
- PUFAs >2 g/day
- Ursodeoxycholic acid.

The following medications are permitted under the condition of no qualitative change (i.e., implementation of a new antidiabetic drug) in the 6 months prior to diagnostic liver biopsy and up to Randomization:

- Insulin
- Sulfonylureas
- Metformin
- Gliptins
- SGLT2-inhibitors
- GLP-1 agonists.

Dose changes are allowed for these medications, except for GLP-1 agonists, which must be on stable dose in the 6 months prior to diagnostic liver biopsy and up to randomization.

In addition, no initiation of SGLT2-inhibitors and GLP-1 agonists is allowed from at least 6 months prior to the diagnostic liver biopsy up to 72 week of treatment (V7).

Patients on sulfonylureas and insulin are recommended to self-monitor blood glucose.

7.12.4. Permitted medication

Any medications other than those listed above are permitted. However, the dosage of a current medication for a chronic disease should remain unchanged as far as possible in order to reduce the risk of unknown DDIs.

In the event that additional concomitant therapy becomes necessary during the study, this should be recorded by the Investigator in the eCRF. This includes drugs used on a chronic as well as on an "as-needed" basis. Patients should be discouraged from starting any new medication without consulting the Investigator unless the new medication is required for emergency purpose.

8. ADVERSE EVENT AND TOXICITY MANAGEMENT

8.1. DEFINITIONS

8.1.1. Adverse events

Any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical (investigational) product and which does not necessarily have to have a causal relationship with this treatment will be considered as an AE. The term AE is synonymous with the term "adverse experience" as used by the FDA.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding or physiological observation, for example), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal product.

Examples of AE include (but are not limited to): abnormal test findings; clinically significant symptoms and signs; changes in physical examination findings; hypersensitivity; progression/worsening of pre-existing condition or underlying disease; recurrence of a pre-existing condition; lack of effect, complication, and termination of pregnancy.

Additionally, they may include the signs or symptoms resulting from: drug overdose, drug withdrawal, drug abuse, drug misuse, drug interactions, drug dependency, extravasation, exposure in utero.

The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

- Test result is associated with accompanying symptoms
- Test result requires additional diagnostic testing or medical/surgical intervention
- Test result leads to a change in trial dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy
- Test result is considered to be an AE by the Investigator or Sponsor.

Repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

An AE does not include the following:

- Medical or surgical procedures performed; the condition that leads to the procedure may be an AE if applicable
- Pre-existing disease, condition or laboratory abnormalities present or detected before the Screening Visit that do not worsen
- Overdose without clinical sequelae

- Any medical condition, or clinically significant laboratory abnormality with an onset before the consent form is signed. Such as medical condition is considered to be pre-existing and should be documented on the medical history of the eCRF
- Uncomplicated pregnancy
- An induced elective abortion to terminate a pregnancy without medical reason
- Events that are identified as efficacy endpoints for the long-term evaluation (described in Section 1.9.2) should not be reported as AE.

The questions concerning whether the condition existed before the start of the active phase of the study and whether it has increased in severity and/or frequency will be used to determine whether an event is a treatment-emergent AE. An AE is considered to be treatment emergent if (1) it is not present when the active phase of the study begins and is not a chronic condition that is part of the patient's medical history, or (2) it is present at the start of the active phase of the study or as part of the patient's medical history, but the severity or frequency increases during the active phase. The active phase of the study begins at the time of the first dose of the study drug. The active phase of the study ends at the last study visit.

8.1.2. Serious adverse events

A SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (see Section 8.1.2.1)
- Requires inpatient hospitalization or prolongation of existing hospitalization (see Section 8.1.2.2)
- Results in persistent or significant disability/incapacity (see Section 8.1.2.3)
- Is a congenital anomaly/birth defect (including fetal malformations associated with spontaneous abortions or elective abortions)
- Is another medically important condition (see Section 8.1.2.4).

In addition, any illnesses reported before starting active treatment or AE meeting the criteria of seriousness (as defined above) and considered to be possibly related (according to the Investigator) to any study-specific procedure (e.g., laboratory testing procedure, liver biopsy) must be reported as an SAE.

8.1.2.1. Life-threatening adverse events

- A life-threatening AE in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

8.1.2.2. *Inpatient or prolonged hospitalization*

An inpatient hospitalization or prolongation of a hospitalization means that the patient stays overnight in the hospital. An overnight stay is defined by hospitalization of 24 hours. Visits to the emergency room will

not be considered hospital admission. Pre-planned hospital stays or hospital stays for nonmedical social reasons will not be considered as hospitalization, for example:

- Hospitalization or prolongation of hospitalization is needed for a procedure required by the protocol. Day or night survey visits for biopsy or surgery required by the protocol are not considered serious.
- Hospitalization or prolongation of hospitalization is part of a routine procedure followed by the study center (e.g., stent removal after surgery). This should be recorded in the study file.
- Hospitalization for survey visits or annual physicals fall in the same category.
- Hospitalization planned before the start of the study for a pre-existing condition that has not worsened does not constitute an SAE (e.g., elective hospitalization for a total knee replacement due to a pre-existing condition of osteoarthritis of the knee that has not worsened during the study).

8.1.2.3. Significant or incapacitating disability

Only a persistent or significant or incapacitating disability is intended. This item refers to a substantial disruption of a person's ability to conduct normal life functions. Thus, disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma.

8.1.2.4. Medically important conditions

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

Examples of such events are:

- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias or convulsions that do not result in hospitalization
- Development of drug dependency or drug abuse.

8.1.3. Clarification on serious adverse events:

- Events that are identified as primary efficacy endpoints for the long-term evaluation should not be included as an AE.
- Death is an outcome of an AE, not an AE in itself.
- An SAE may occur even if the patient was not being treated with the investigational medicinal product at the occurrence of the event.

- Life-threatening means that patient is at immediate risk of death. This does not include an event that might have led to death if it had occurred with greater severity.
- Complications that occur during hospitalizations are AEs. If a complication prolongs the hospitalization, it is a SAE.
- Patient hospitalization means that the patient stays overnight in the hospital. Pre-planned hospital stays or hospital stays for nonmedical social reasons will not be considered as hospitalization.
- A procedure for protocol/disease-related investigations (e.g., biopsy) should not be reported as SAE. Hospitalization or prolonged hospitalization for a complication of such procedures should be reported as SAE.

8.1.4. Adverse drug reaction

An adverse drug reaction (ADR) is defined as a response to a medicinal product which is noxious and unintended and that is considered casually related to an investigational medicinal product. A serious ADR (SADR) is an ADR which meets the seriousness criteria.

8.1.5. Unexpected adverse event

Expectedness is assessed by the Sponsor. An unexpected AE is defined as an event that has a nature of severity or specificity that is not consistent with the applicable Investigator Brochure or that is symptomatically and pathophysiologically related to a known toxicity but differs because of a greater severity or specificity.

"Unexpected" refers to an ADR that has not been previously observed and reported rather than an event that has not been anticipated based on the properties of the drug.

8.2. ASSESSMENTS

The Investigator will establish whether or not any AE have occurred at each visit from the date of consent. The patient will be questioned in a general manner to determine specific symptoms without offering the patient any suggestion.

8.2.1. Intensity assessment

The intensity of the AE will be graded as follows:

- **Mild**: Awareness of signs or symptoms, but easily tolerated and are of minor irritant type causing no loss of time from normal activities. Symptoms do not require therapy or a medical evaluation; signs and symptoms are transient.
- **Moderate**: Events introduce a low level of inconvenience or concern to the participant and may interfere with daily activities, but are usually improved by simple therapeutic measures; moderate experiences may cause some interference with functioning.

- **Severe**: Events interrupt the participant's normal daily activities and generally require systemic drug therapy or other treatment; they are usually incapacitating.

8.2.2. Relation to the study treatment

The Investigator will make a clinical and scientific judgment regarding whether or not the AE was related to study treatment. The Investigator will evaluate any changes in laboratory values, make a determination as to whether or not the change is clinically important, and whether or not the changes were related to study drug. However, even if the Investigator feels there is no relationship to the study drug, the AE or clinically significant laboratory abnormality must be recorded in the eCRF.

The Investigator will record the relation to the study treatment according to the following causality terms:

- **Related:** the AE follows a reasonable temporal sequence from the time of drug administration and it cannot be explained by the patient's clinical state or the study procedures/conditions. The AE abates upon discontinuation of the study drug and reappears when the study drug is introduced.
- **Possibly related:** the AE follows a reasonable temporal sequence from the time of drug administration, but could have been produced by the patient's clinical state or the study procedures/conditions.
- **Unlikely related:** the temporal association between the AE and the study drug is such that the study drug is not likely to have any reasonable association with the AE. The relationship is not likely because of other plausible explanations.
- **Not related:** the AE must definitely be caused by the patient's clinical state or the study procedure/conditions. A reasonable explanation must be given, e.g., no investigational product taken, preplanned elective medical intervention, or incompatible temporal relationship.
- **Not assessable**: the report suggesting an adverse reaction cannot be judged because information is insufficient or contradictory and data cannot be supplemented or verified.

8.2.3. Action taken and outcome

The Investigator will record the action taken with drug and outcome of the event for each AE according to the following:

<u>Action taken with investigational drug</u>

- Drug permanently withdrawn – in case a patient is permanently withdrawn from the study drug
- Drug temporarily withdrawn – in case the study drug is temporarily withdrawn
- Dose not changed – in case no action is taken regarding the study drug
- Unknown
- Not applicable – an AE started before initiation of treatment with study drug, the treatment had been completed prior to reaction/event, or the patient has died.

Outcome

- Recovered/resolved
- Recovering/resolving
- Not recovered/not resolved
- Recovered/resolved with sequelae
- Fatal
- Unknown.

Note: In case of irreversible congenital anomalies the choice not recovered/not resolved should be used. "Fatal" should be used when death is possibly related to the reaction/event.

8.3. REPORTING

8.3.1. Reporting an adverse event

All AEs regardless of seriousness or relationship to study drug, including those occurring during the Screening Period, are to be recorded on the corresponding page(s) of the eCRF and in the patient's medical record from the ICF signature until study end for each patient. Whenever possible, symptoms should be grouped as a single syndrome or diagnosis. The Investigator should specify the date of onset, maximal intensity, action taken with respect to study drug, corrective therapy given, outcome, and his/her opinion as to whether there is a reasonable possibility that the AE was caused by the study drug.

Adverse event reporting begins from signature of the patient ICF at the first Screening Visit and ends at study end for each patient.

8.3.2. Reporting a serious adverse event

Serious AE reporting begins from signature of the patient ICF and ends at study end for each patient.

Any SAE that is brought to the attention of the Investigator at any time after the reporting period and which is considered by him/her to be caused by the study drug within a reasonable possibility, should be reported.

Any of the portal hypertension/cirrhosis related events described in Section 2.1.1 that are identified as potential primary efficacy endpoints for long-term evaluation will NOT be reported as SAEs unless it is determined by the adjudication committee that the event does not meet the predefined criteria for an endpoint. Events that are identified as potential primary efficacy endpoints for long-term evaluation that are not confirmed by adjudication will be reported as described with the start of the reporting time window being the time of negative adjudication decision.

Investigators must notify, by fax or e-mail, the Sponsor designated representative [redacted] of all SAEs **IMMEDIATELY (within 24 hours of the Investigator becoming aware of the event).**

ANY SERIOUS ADVERSE EVENTS, WHETHER OR NOT RELATED TO THE STUDY DRUG, MUST BE REPORTED IMMEDIATELY (WITHIN 24 HOURS) TO [redacted] AT THE FOLLOWING FAX NUMBERS:

FAX numbers: [redacted]

Contact Person: [redacted]

E-mail: [redacted]

All SAEs independent of the circumstances or suspected cause must be reported in ENGLISH on a SAE Form. The SAE Form should include a clearly written narrative describing signs, symptoms, and treatment of the event, diagnostic procedures, as well as any relevant laboratory data and any sequelae, in order to allow a complete medical assessment of the case and independent determination of the possible causality.

The Investigator is also required to submit follow-up SAE reports to [redacted] within 24 hours of becoming aware of additional information such as diagnosis, outcome, causality assessment, results of specific investigations, and any new significant information that has not been previously reported.

It is critical that the information provided on the initial or follow-up SAE Form matches the information recorded in the source documents and the eCRF for the same event.

Copies of additional laboratory tests, consultation reports, postmortem reports, hospital case reports, autopsy reports, and other documents should be sent when requested and applicable. All provided reports must be anonymized.

Follow-up reports relative to the patient's subsequent course must be submitted to [redacted] until the event has subsided or, in case of permanent impairment, until the condition stabilizes.

The Sponsor or its designated representative will report all the relevant safety information to the concerned Competent Authorities and to the Independent Ethics Committee(s) (IRB/IEC) concerned according to the country-specific requirements.

Investigator must fulfill his/her regulatory obligations to the Regulatory Authorities and/or to the Ethics Committee in accordance with local regulations.

Depending on local regulations in different regions and countries, the Sponsor or designated clinical research organization (CRO) may be required to expedite report to the Regulatory Authorities for:

- SAEs (including events related to study procedures)
- SADRs
- Suspected unexpected serious adverse reactions (SUSARs)

Each SAE report received from the Investigators will be evaluated by the designated CRO for pharmacovigilance who will assess the seriousness of the event. Each SAE report will be evaluated by the Sponsor and/or his designees who will assess the relationship to study procedure or study treatment and the expectedness of the event. Expectedness will be assessed using the reference safety information included in the Investigator Brochure.

Any unexpected safety issue that changes the risk benefit analysis and is likely to have an impact on the patients who have participated in the trial will be reported by the Sponsor as soon as possible to the Competent Authority(ies) concerned together with proposed actions.

8.3.3. Follow-up

The Investigator should take all appropriate measures to ensure the safety of the patients, notably he/she should follow up the outcome of any AE until the return to normal or until stabilization of the patient's condition.

The patient must be followed up until clinical recovery is complete and laboratory results have returned to normal, or until progression has been stabilized. This may imply that follow-up will continue after the patient has left the study and that additional investigations may be requested by the Sponsor. This information should be documented in the patient's medical records.

8.4. POST STUDY REPORTING REQUIREMENTS

Any SAEs and deaths that occur within 30 days of the last dose of the study drug, regardless of causality, should be reported.

Any SAE that is brought to the attention of the Investigator at any time after the reporting period and which is considered by him/her to be caused by the study drug within a reasonable possibility, should be reported.

8.5. CLINICAL LABORATORY ABNORMALITIES AND OTHER ABNORMAL ASSESSMENTS AS ADVERSE EVENTS OR SERIOUS ADVERSE EVENTS

Laboratory abnormalities are not necessarily recorded as AEs or SAEs. However, laboratory abnormalities that are considered clinically relevant by the Investigator must be recorded as an AE or SAE as applicable.

8.6. SPECIAL SITUATION REPORTS

Special situations reports include pregnancy reports, reports of medication error, abuse, misuse or overdose, and reports associated with product complaints.

8.6.1. Pregnancy

In case of pregnancy a communication will be sent by the Investigator to [redacted] by faxing a completed pregnancy form within 24 hours of his/her knowledge of the pregnancy.

Pregnancies of females partners of male patients exposed to study medication should also be reported to [redacted] using the corresponding pregnancy form, provided that pregnant female partners have signed an informed consent.

Female patients must be instructed to discontinue the study drug immediately and inform the Investigator as soon as possible once they are aware of being pregnant or suspect that they are pregnant during the study or within 30 days of the last dose of the study drug.

Female patients will be requested, as part of the general ICF, to provide informed consent to allow reasonable attempts to be made to obtain information on any possible medicinal product exposure to an embryo or fetus and to follow up on the outcome of the pregnancy.

The Investigator will contact the patient at the expected time of delivery for follow-up. If the outcome of pregnancy meets the criteria for immediate classification of an SAE (e.g., spontaneous or therapeutic abortion, stillbirth, neonatal death, congenital anomaly, birth defect), the Investigator should follow the procedure for reporting SAEs as detailed in Section 8.3.2.

The pregnancy itself is not considered an AE.

8.6.2. Medication error

Medication error is defined as an unintentional error in the prescribing, dispensing, or administration of a medicinal product while in the control of the healthcare professional, patient, or consumer. All medication errors will be documented in the eCRF and, in case of any potential risk to patient safety, would be reported as appropriate (see Section 8.3).

8.6.3. Misuse

This refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the authorized product information and will be reported in the eCRF. All misuse will be documented in the eCRF and, in case of any potential risk to patient safety, would be reported as appropriate (see Section 8.3).

8.6.4. Overdose

This refers to the administration of a quantity of a medicinal product given per administration or cumulatively, which is above the maximum recommended dose according to the authorized product information (see Section 8.1.1 and Section 8.3.1). Clinical judgment should always be applied.

8.6.5. Abuse

This corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

9. STATISTICAL METHODS AND DATA ANALYSIS

This section is an overview of the key elements of the statistical analysis for this study. Further details on statistical reporting and analyses will be contained in a separate statistical analysis plan (SAP). This SAP may be revised during the study only to accommodate protocol amendments and to make changes to adapt to unexpected issues in study execution and data collection that could affect planned analyses. In all circumstances, a final SAP should be issued prior to database lock and treatment unblinding. The first approved version of the SAP should be available within 3 months of first patient randomized and before the first DSMB meeting.

The main analyses will be based on patients with fibrosis stage F2 and F3. The summaries will be repeated in an exploratory manner with the inclusion of patients with fibrosis stage F1.

9.1. RANDOMIZATION AND TREATMENT ASSIGNMENT

Random allocation will be made to the 2 treatment groups (elafibranor and placebo) in a 2:1 ratio basis and stratified by the following factors:

- Type 2 diabetes (yes, no)
- Gender (male, female) (with a capping of women to 40%)
- Fibrosis stage (F1, F2, F3) (capped to 202 F1 patients).

Details on the randomization process are in Section 3.2.

9.2. ENDPOINTS

9.2.1. Surrogate endpoint - resolution of NASH

The first surrogate endpoint for this study is resolution of NASH without worsening of fibrosis after 72 weeks of treatment. Resolution of NASH is defined as the disappearance of ballooning (i.e., grade 0) and disappearance or persistence of minimal lobular inflammation (i.e., grade 0 or 1) with an overall pattern of injury not qualifying for steatohepatitis. Worsening of fibrosis is evaluated using NASH CRN fibrosis staging system and defined as progression of at least 1 stage. This surrogate endpoint will be formally assessed at the time of the surrogate efficacy analysis when at least 1023 of the F2 to F3 patients complete the 72 week treatment period or discontinue early from the study (see Section 9.8.1 for details). An additional exploratory analysis of this endpoint will take place at the time of the final analysis.

9.2.2. Long-term endpoint – time to clinical event/death

The long term endpoint of clinical outcomes is a composite endpoint composed of death due to any cause, liver cirrhosis, and the full list of portal hypertension/cirrhosis related events:

- Liver transplantation
- MELD score ≥15

- HCC
- the onset of:
    - variceal bleed
    - hepatic encephalopathy
    - spontaneous bacterial peritonitis
    - ascites
    - hepatorenal syndrome
    - hepatopulmonary syndrome
    - chronic gastrointestinal blood loss due to portal hypertensive gastropathy (provided that these lead to hospitalization or transfusion).

The final analysis will be performed when 456 patients experience an event listed above. This is expected to occur approximately 72 months after the first patient is randomized.

9.2.3. Key Secondary Endpoint

The key secondary endpoint is:

- Percentage of patients with improvement of fibrosis of at least 1 stage according to NASH CRN scoring at 72 weeks.

This key secondary endpoint will be assessed at the time of the surrogate endpoint analysis (at least 1023 patients with fibrosis stage F2 and F3) for the resolution of NASH without worsening of fibrosis endpoint.

9.2.4. Other Secondary Endpoints

The other secondary endpoints are:

- To assess histological changes after 72 weeks of treatment and follow-up biopsy on the following endpoints:
    - percentage of patients with resolution of NASH without worsening of fibrosis (follow-up biopsy)
    - percentage of patients with improvement of fibrosis of at least 1 stage according to NASH CRN scoring
    - percentage of patients with at least 1 point improvement in histological scores (NASH CRN scoring: total NAS, steatosis, hepatic ballooning, lobular inflammation), fibrosis (NAFLD Ishak scoring system), or portal inflammation
    - percentage of patients improvement of NAS of at least 2 points
    - percentage of patients with at least a 1 point improvement in SAF activity score
    - mean changes in NAS, steatosis, hepatic ballooning, lobular inflammation, portal inflammation, SAF activity score
    - changes in area of fibrosis by morphometry

  - mean changes in fibrosis using NASH CRN and NAFLD Ishak scoring.
- To assess the following endpoints at Week 72 and at the end of the LTTP:
  - changes in liver enzymes and liver markers
  - changes in noninvasive markers of fibrosis and steatosis
  - changes in lipid parameters
  - variation in body weight
  - changes in insulin resistance and glucose homeostasis markers
  - changes in inflammatory markers
  - changes in cardiovascular risk profile as assessed by Framingham scores
  - changes in quality of life (SF-36 questionnaire).
- To assess the onset to:
  - liver cirrhosis
  - death of any cause
  - any portal hypertension or cirrhosis related events
  - cardiovascular events
  - liver-related death events.

9.2.5. Exploratory endpoints

The exploratory endpoint is:

- To constitute a biobank for discovery and validation of biomarkers in NASH.

Details on all endpoints will be given in the SAP.

9.3. ANALYSIS SETS

The following analysis sets will be used in this study:

- Enrolled: all patients who sign informed consent. This set will be used to summarize disposition.
- ITT: all randomized F2 and F3 patients. This set will be used to summarize efficacy. The main analysis of the primary and key secondary endpoints will be based on the ITT.
- Safety set (SS): all randomized F2 and F3 patients who receive at least 1 dose of study drug. This set will be used to summarize safety.
- Per protocol set (PPS): all F2 and F3 patients who receive at least 1 dose of study drug and do not have any important protocol deviations leading to exclusion from the PPS. Important protocol deviations will be defined in the SAP and agreed prior to database lock. Supportive analysis of the primary and key secondary endpoints will be based on the PPS.
- Exploratory F1 cohort: All randomized F1 patients who have taken at least 1 dose of study drug.
- Full Intent-To-Treat Set (FITT): all randomized patients.
- Full Safety Set (FSS): all randomized patients who receive at least 1 dose of study drug.

Patients in the ITT, FITT, PPS, and exploratory F1 cohorts (study population and efficacy data) will analyzed based on randomized treatment. Patients in the SS, FSS, and exploratory F1 cohorts (safety data) will be analyzed based on actual treatment received.

9.4. ANALYSIS OF PRIMARY ENDPOINTS

9.4.1. Resolution of NASH

The null hypothesis for resolution of NASH without worsening of fibrosis is that there is no difference in response rates between the elafibranor and placebo groups. The alternative hypothesis is that there is a difference in response rates between the elafibranor and placebo groups. The null hypothesis will be tested at the two-sided 0.01 alpha level.

The number and percentage of patients with resolution of NASH without worsening of fibrosis at the end of the 72 week treatment period will be summarized by treatment group. The main analysis will be performed using a logistic regression model, with fixed terms for treatment, type 2 diabetes (yes, no), gender (male, female), fibrosis stage (F2, F3) and baseline NAS. The statistical model will be used to calculate the odds ratio (elafibranor/placebo) and 99% confidence interval. The main confirmatory analysis will be performed when at least 1023 F2/F3 patients have completed the 72 week treatment period or discontinued from the study. The main analysis will be based on the ITT. Supportive analysis will be based on the PPS.

Patients with missing data for resolution of NASH without worsening of fibrosis will be treated as a nonresponder for the main analysis. Additional sensitivity analysis using multiple imputations and a pattern mixture model will be performed. Further details will be provided in the SAP.

9.4.2. Long-term endpoints

The null hypothesis is that there is no difference in the hazard ratio between the elafibranor and placebo treatment groups. The alternative hypothesis is that there is a difference in the hazard ratio between the elafibranor and placebo treatment groups. The null hypothesis will be tested at the two-sided 0.04 alpha level.

The data will be analyzed using a Cox proportional hazards model with fixed terms for treatment, type 2 diabetes, gender, fibrosis stage, and baseline NAS. The Cox proportional hazards model will be used to calculate the hazard ratio (elafibranor/placebo) and 96% confidence interval. This will be performed when at least 456 patients experience a clinical event/death. The time to clinical event/death and time to first cardiovascular event death will also analyzed using an unadjusted Cox-proportional hazard's model, log rank test and a nonparametric randomization based analysis of covariance method proposed by Saville and Koch.[36]

The time to clinical event/death will be presented graphically using a Kaplan-Meier curve. The median time to first clinical event/death and 95% confidence interval will also be presented for each treatment group.

Missing data will be censored at the last known date.

The main analysis will be based on the IIT. Supportive analysis will be based on the PPS.

9.5. OTHER STATISTICAL ANALYSIS

9.5.1. Key secondary endpoint

The number and percentage of patients with improvement of fibrosis according to NASH CRN scoring at the end of the 72 week treatment period will be summarized separately by treatment group. The data will be analyzed using a logistic regression model, with fixed terms for treatment, type 2 diabetes, gender, fibrosis stage and baseline NAS by NASH CRN scoring. The analysis will be performed at the time of the surrogate endpoint analysis when at least 1023 of patients with fibrosis stage F2 and F3 have completed the 72 week treatment period or discontinued from the study. The null hypothesis will be tested at the two-sided 0.01 alpha level.

The main analysis will be based on the IIT. Supportive analyses will be based on the PPS.

9.5.2. Other secondary endpoints

All other secondary endpoints will be summarized by treatment group using descriptive statistics. The main analysis will be based on the ITT.

Categorical endpoints will be analyzed using a logistic regression model in the same manner as resolution of NASH without worsening of fibrosis.

Time to event endpoints will be analyzed using the Cox proportional hazard's model in the same manner as time to clinical event/death.

Continuous endpoints will be analyzed using an Analysis of Covariance (ANCOVA) model with fixed terms for treatment, type 2 diabetes, gender, fibrosis stage, and baseline NAS. An unstructured covariance matrix will be used for this analysis. The statistical model will be used to calculate the mean treatment difference and 95% confidence interval. If the data does not meet the required assumptions for parametric tests, the data will be analyzed using a nonparametric analysis of covariance method of Zink and Koch.[37]

Further details will be in the SAP.

9.5.3. Subgroup analyses

Exploratory analyses of the primary and key secondary endpoints will be done for selected subgroups, including, but not limited to, the following:

- Presence of type 2 diabetes (yes, no)
- Gender (male, female)

- Fibrosis (F2, F3)
- Geographic region (North America, Europe, South America, Rest of World)
- Race (Caucasian, Other)
- Ethnicity (Hispanic, not Hispanic)
- Age (<60, ≥60 years).

Forest plots will be generated for each of these endpoints for patients in the ITT population.

9.5.4. Exploratory analyses

Additional exploratory analyses of the efficacy data will be performed on the exploratory F1 cohort.

9.6. STRATEGIES TO CONTROL TYPE I ERROR

The overall type I error for the primary endpoints in this study is two-sided α=0.05. The alpha for the primary endpoints will be split 20%/80%, with two-sided α=0.01 for resolution of NASH and two-sided α=0.04 for time to clinical event/death.

A hierarchical gate-keeping strategy will be used to control for multiplicity for the key secondary endpoint. If the resolution of NASH without worsening of fibrosis endpoint is statistically significant, the key secondary endpoint, improvement of fibrosis according to NASH CRN scoring, will be tested in a confirmatory manner with a two-sided α=0.01.

Statistical testing for all other secondary endpoints will be of exploratory nature.

As this is a single pivotal study that will be used for a regulatory submission, the consistency of the results for the primary and key secondary endpoints will be further explored by population and selected subgroups. In addition, different approaches will be applied for dealing with missing data.

9.7. SAMPLE SIZE CALCULATION

All sample size calculations were done in EAST 6.3.

9.7.1. Resolution of NASH

The following assumptions were made for the sample size calculation for resolution of NASH:

- α=0.01 two-sided
- Randomized patients with no response assessment at Week 72 will be counted as nonresponders
- Pooled variance
- Randomization ratio of 2:1 (elafibranor: placebo)
- 8% response in the control group
- 16.5% response in the elafibranor group.

The 8% response rate in the placebo group (calculated as the mean response rate based on the Phase II FLINT study[35] [subanalysis including only patients with stage 2 and stage 3 fibrosis or stage 1 fibrosis with diabetes, obesity or ALT ≥ 60 {associated with fibrosis progression}; placebo response rate 6.5%] and the GFT505-212-7 placebo data [11% response rate for patients with any stage fibrosis {F1; F2; F3} and 7% response rate for patients with only stage 2 and 3 fibrosis]). The 16.5% response rate in the elafibranor group is based on the Phase II GFT505-212-7 elafibranor data (calculated as the mean response rate based on a 20% response rate for patients with any stage fibrosis ([F1; F2; F3] and 13% response rate for patients with only stage 2 and 3 fibrosis).

Based on these assumptions, a sample size of 1023 patients provides 90% power to show that elafibranor is superior to the placebo with respect to resolution of NASH without worsening of fibrosis.

9.7.2. Time to clinical event/death

The following assumptions were made for the sample size calculation for time to clinical event/death:

- 24 month enrollment (with an 18-month ramp up to as many as 200 patients per month)
- 72 month maximum follow-up
- α=0.04 two-sided
- Annual event rate of 7% for the placebo group
- Hazard ratio of 0.75 in favor of the elafibranor group
- 4% annual drop-out rate over 72 months
- Randomization ratio of 2:1 (elafibranor: placebo).

The 7% annual event rate in the placebo group is based on published literature on developing cirrhosis in patients with NASH and advanced fibrosis (F2-F3).[21,22,23,24,25] The rate of developing cirrhosis was estimated to be 7% (based on 8% per year in F3 patients and 6% per year in F2 patients). In a conservative approach, no additional event rate was added for other events than histological cirrhosis or cirrhosis decompensation events. An annual clinical event/death rate of 7% was thus defined for the composite of both these endpoints.

There is no long-term randomized clinical trial in a NASH population with moderate and severe liver fibrosis. In the 72-week FLINT trial, the total drop-out rate was 6.7%.[35] Therefore, we estimate an approximate annual drop-out rate of 4%. Based on these assumptions, 456 events are required to provide 80% power to show that elafibranor is superior to placebo with respect to time to clinical event/death. In order to obtain 456 events, at least 2022 patients will be required in the IIT.

9.8. SAFETY ANALYSIS

Safety data (exposure, AEs, clinical laboratory tests, vital signs, and ECGs) will summarized by treatment group using descriptive statistics. The main summaries of safety will be based on the SS. Additional safety analysis will be based on the FSS and the exploratory F1 cohort.

Adverse events will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA). An overall summary of AEs will be provided. The number and percentage of patients reporting AEs will also be presented by MedDRA System Organ Class and preferred term. The AEs will be summarized by worst severity and relationship to study drug. Serious AEs, and AEs leading to discontinuation will also be summarized. Narratives will be added for all SAE.

Clinical laboratory tests (hematology, chemistry, and urinalysis) recorded at each timepoint and change from baseline will be summarized by treatment group using descriptive statistics. Clinical laboratory values for each parameter will be assigned a classification according to whether the value is lower than, within, or higher than the reference range for that parameter. The values will then be summarized using shift tables to evaluate categorical changes from baseline to end of the 72 week treatment period with respect to reference ranges. The number and percentage of patients reporting markedly abnormal clinical laboratory values will also be summarized by treatment group.

Liver and kidney related laboratory tests including an assessment of DILI will also be summarized.

Vital signs recorded at each timepoint and change from baseline will be summarized by treatment group using descriptive statistics.

9.8.1. Surrogate endpoint analysis

The analysis of resolution of NASH without worsening of fibrosis will occur when 1023 F2 and F3 patients complete 72 weeks of treatment or discontinue early from the study. The null hypothesis will be tested at the two-sided 0.01 alpha level.

At this time, a snapshot of the database will be cleaned and locked for analysis and potential Subpart H or conditional approval submission. This analysis will be done by an unblinded team separate from the study team; the study team will not be unblinded until the final analysis at the end of follow-up.

The DSMB will also periodically review safety data from the study to ensure the well-being of study participants. These safety reviews will be based on reports generated by the SAC and may include select efficacy results so that the DSMB can assess the likely benefit-risk profile of elafibranor. These are not considered a formal interim analysis, and no type I error adjustments will be done for these reviews. Details will be in the DSMB Charter.

9.9. INTERIM ANALYSIS

An adaptive design interim analysis will be performed after 140 primary events (approx. 30% of the 456 required events) have been accrued. The interim analysis will be performed by an unblinded team separate from the study team. The Data Safety Monitory Board (DSMB) will review the interim analysis results and provide final recommendations regarding trial termination due to futility and adjustment of the target number of primary events. Details will be in the DSMB Charter and SAP.

10. DATA HANDLING AND RECORD KEEPING

10.1. CASE REPORT FORM AND SOURCE DOCUMENTS

A case report form (CRF) is required and should be completed for each screened patient. The completed eCRFs are the sole property of the Sponsor and should not be made available in any form to third parties, except for authorized Sponsor's representatives or appropriate regulatory authorities, without written permission from the Sponsor.

The Investigator will ensure that all data are entered promptly, legibly, completely, accurately and conform to source documents, in accordance with specific instructions accompanying the eCRFs designed specifically for this study. The CRF being used for this study is an electronic CRF that has been fully certified as being compliant with the FDA regulations at 21 Code of Federal Regulations (CFR) Part 11.

All study required patient data generated during the study will be recorded in the eCRF, with the exception of SAE forms and SF-36 which will be collected via ePRO (which is then transferred to the electronic data capture). Patients will not be identified by name in the eCRF or on any study documents to be collected by the Sponsor (or designee), but will be identified by a patient number.

The Investigator will review and approve each completed eCRF; the Investigator's validation serving as attestation of the Investigator's responsibility for ensuring that all clinical and laboratory data entered in the eCRF are complete, accurate, and authentic.

Should a correction be made, the corrected information will be recorded in the eCRF by the authorized person and explained (if necessary). All corrected data will be tracked through an audit trail.

It is the Investigator's obligation to ensure documentation of all relevant data in the patient's medical file (medical history, concomitant diseases, patient identification number, date of informed consent, visit dates, administration of study medication, AEs [start and stop dates] and all concomitant medications [start and stop dates]). All data recorded in the eCRF will be documented by source data.

10.2. RETENTION OF RECORDS

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified.

The Investigator will be provided with a study file, which should be used to file the Investigator Brochure, protocol/amendments, drug accountability records, sample informed consent, staff curriculum vitae, correspondence with the IRB/IEC, Sponsor, and other study-related documents.

To enable evaluations and/or audits from regulatory authorities or the Sponsor, the Investigator agrees to keep records, including the identity of all participating patients, all original signed ICFs, copies of all eCRFs, source documents, and detailed records of treatment disposition.

The Investigator must retain the study documentation until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. However these documents should be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the Sponsor. All hospital records will be archived according to local regulation.

The Sponsor should be notified if the Investigator relocates, retires, or for any reason withdraws from the trial. The trial records must be transferred to an acceptable designee, such as another Investigator, another institution, or to the Sponsor.

11. QUALITY CONTROL AND QUALITY ASSURANCE

11.1. QUALITY CONTROL & MONITORING PROCEDURES

It is the responsibility of the Investigator to ensure that the study is conducted in accordance with the protocol, Good Clinical Practice (ICH topic E6), applicable regulatory requirements, and the current Declaration of Helsinki (APPENDIX I: World Medical Association Declaration of Helsinki) and that valid data are entered into the eCRFs.

To achieve this objective, the Study Monitor's duties are to aid the Investigator and, at the same time, the Sponsor in the maintenance of complete, legible, well-organized, and easily retrievable data.

Before enrolling any patients in this study, the Study Monitor will review the protocol, the brochure for clinical investigators, the eCRFs and instructions for their completion and return, the procedure for obtaining informed consent, and the procedure for reporting AEs and SAEs with the Investigator. In addition, the Study Monitor will explain the Investigator's reporting responsibilities and all applicable regulations concerning the clinical evaluation of the study drug.

The Investigator will permit the representatives of Sponsor to monitor the study as frequently as the Sponsor deems is necessary to determine that data recording and protocol adherence are satisfactory. A Study Monitor from [redacted] Late Stage Development Services will be responsible for monitoring this clinical trial. To this end, the Study Monitor will visit the study site at suitable intervals and be in frequent contact through verbal and written communication. The eCRFs and related source documents, as well as drug accountability will be reviewed in detail by the monitor at each visit, in accordance with relevant SOPs and Good Clinical Practice (GCP; ICH topic E6) regulations. This includes results of tests performed as a requirement for participation in this study and any other medical records required to confirm information contained in the eCRFs, such as past medical history and secondary diagnoses.

A risk based monitoring strategy will be used for this study. Study monitoring strategy design will be based on overall study risk assessment. Individual site monitoring strategy design will be based on individual site risk assessment. On site monitoring will focus on source document verification of mandatory and critical data and source document review of critical processes, and will be supported by formal remote site monitoring activities. Centralized monitoring activities will review study data to assess changes in individual site risk and to identify emerging trends, risks and issues across sites, countries, regions, and the global study. Further details can be found in the Monitoring Plan.

It is essential that the Study Monitor has access to all documents (related to the study and the individual participants) at any time these are requested. In turn, the Study Monitor will adhere to all requirements for patient confidentiality as outlined in the ICF. The Investigator and Investigator's staff will be expected to cooperate with the Study Monitor, to be available during a portion of the Monitoring Visit to answer questions, and to provide any missing information.

All monitoring activities will be reported and archived in the Trial Master File.

11.2. ETHICAL PRINCIPLES

This protocol complies with the principles laid down by the 18th World Medical Assembly (Helsinki, 1964) and all applicable amendments laid down by the World Medical Assemblies (APPENDIX I: World Medical Association Declaration of Helsinki), and the GCP guideline.

This trial also complies with applicable local regulatory requirements and laws of each country in which the study is performed, as well as any applicable guidelines.

11.3. QUALITY ASSURANCE

For the purpose of ensuring compliance with the protocol, GCP and applicable regulatory requirements, the Investigator should permit auditing by the Sponsor and/or designee and inspection by applicable regulatory authorities. The Investigator agrees to allow the auditors/inspectors to have direct access to his/her study records for review, being understood that these personnel will adhere to all requirements for patient confidentiality, and as such will not disclose any personal identity or personal medical information.

As soon as the Investigator is notified of a future inspection by the Authorities, he/she will inform the Sponsor and authorize the Sponsor to participate at this inspection.

The confidentiality of the data verified and the anonymity of the patients should be respected during these inspections.

Clinical data associates from the Sponsor's representative will review the data for completeness and logical consistency. Additionally, the clinical data associates will use automated validation programs to help identify missing data, selected protocol violations, out of range data, and other data inconsistencies. Requests for data clarification or correction will be electronically provided to the investigative site for resolution. Clinical data associates will assure that corrections have been applied properly.

12. ETHICS AND REGULATORY

12.1. INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE

The GCP guidelines and the US CFR Title 21 Section 56 (21 CFR 56) require that approval must be obtained from an Independent Ethics Committee (IRB/IEC) prior to participation of human patients in research studies. Prior to the study onset, the protocol, ICF, advertisements to be used for patient recruitment, and any other written information regarding this study to be provided to the patient or the patient's legally acceptable representative must be approved by the IRB/IEC. The Sponsor will supply relevant material for the Investigator to submit to the IRB/IEC for the protocol's review and approval. Verification of the IRB's unconditional approval of the protocol and the written ICF statement will be transmitted to the Investigator. Documentation of the relevant IRB/IEC approval and of the IRB/IEC compliance with GCP guideline will be maintained by the site and will be available for review by the Sponsor or its designee or by the authorized members of regulatory agencies.

The Applicant must supply the Sponsor with written documentation of the initial favorable opinion of the clinical research before the start of the trial.

The study will not commence until favorable opinion has been obtained from the appropriate IRB/IEC.

If any alterations, other than changes of administrative nature only, are made to the study protocol, a formal protocol amendment will be issued. The IRB/IEC will be informed by the Investigator of subsequent protocol amendments and of SUSARs. Approval for protocol amendments will be transmitted in writing to the Investigator.

The amendment will not be implemented until IRB/IEC approval, except in cases where immediate implementation is necessary to eliminate or prevent imminent hazard to the patients. A protocol change intended to eliminate an apparent immediate hazard must be documented in an amendment, reported to the IRC/IEC within 5 working days, and submitted to the appropriate regulatory agencies in the required time frame.

If requested, the Investigator will permit audits by the IRB/IEC and regulatory inspections by providing direct access to source data/documents.

The Investigator will provide the IRB/IEC with progress reports at appropriate intervals (not to exceed 1 year) and a Study Progress Report following the completion, termination, or discontinuation of the Investigator's participation in the study.

12.2. COMPETENT AUTHORITY

In the same way as for IRB/IEC (see Section 12.1), when required by national regulation, approval from Competent Authorities (CA) should be granted before the beginning of the study. If applicable, Amendments will also be submitted to CA for approval.

12.3. PATIENT INFORMATION AND CONSENT

Written informed consent for the study will be obtained from each patient before protocol-specific procedures are carried out. The ICF used by the Investigator for obtaining the patient's Informed Consent must be reviewed and approved by the Sponsor prior to submission to the appropriate ethics committee (IRB/IEC). The ICF will be approved (along with the protocol) by the IRB/IEC.

In the case of any exploratory substudies, specific study documents will be prepared and IRB/IEC and authority approvals shall be obtained when applicable.

The Investigator or a person designated by the Investigator (according to applicable regulatory requirements), will explain the nature of the study and the action of the test product. The patients will be informed that participation is voluntary and that they can withdraw from the study at any time. In accordance with 21 CFR 50, the informed consent process shall be documented by the use of a written ICF approved by the designated IRB/IEC and will be signed and personally dated by the patient or by the patient's legally acceptable representative and by the person who conducted the informed consent discussion prior to protocol-specific procedures being performed. A separate consent form will be obtained for optional genetic and biomarker samples to be stored in the blood bank.

The Investigator must maintain the original, dated and signed ICF. A copy of the signed ICF must be given to the patient.

12.4. PATIENT CONFIDENTIALITY

The Sponsor will affirm and uphold the principle of the patient's right to protection against the invasion of privacy. Throughout this study and any subsequent data analyses, all data will be identified only by protocol number and patient number.

All unpublished information that the Sponsor gives to the Investigator shall be kept confidential and shall not be published or disclosed to a third party without the prior written consent of the Sponsor.

When the Sponsor generates reports for presentations to regulatory agencies, one or more of the Investigators who has/have contributed significantly to the study will be asked to endorse the final report. The endorsement is required by some regulatory agencies.

The Investigator shall not make a patent application based on the results of this study and shall not assist any third party in making such an application without the written authorization of the Sponsor unless otherwise specified in the CSA.

12.5. DEFINITION OF THE END OF THE RESEARCH

End of the research corresponds to the end of participation (end of study EOT Visit) of the last patient participating in the research.

13. FINANCING AND INSURANCE

13.1. FINANCIAL ISSUES

Financial contracts will be signed between the Sponsor and the Investigator/Institution before initiation of the study.

13.2. INSURANCE AND PATIENT INJURY

The patients taking part in the trial will be covered by the insurance taken by the Sponsor for this trial, if they were to suffer any prejudice as a result of taking part in the trial.

In general, if a patient is injured as a direct result of the study drug, the Sponsor will pay for reasonable and necessary medical treatment for the injury, to the extent the expenses are not covered by the patient's medical insurance, a government program, or other responsible third party. If laws or regulations of the locality in which the trial is taking place require additional payment of expenses, the Sponsor shall comply with such law or regulation.

The Sponsor certifies to have taken out an insurance policy to cover the financial consequences of its civil liability and that of everyone involved in the research, and notably that of the Investigators and their colleagues with regard to any accidents or damage concerning the administration of the drug or paraclinical examinations directly linked to the performance of the trial.

14. STUDY RESULTS AND PUBLICATION POLICY

14.1. STUDY REPORT

The final report will be written in ENGLISH upon completion of study and statistical analysis according to ICH E3 guideline. The report or part of it must be submitted to relevant authorities if applicable.

[redacted] will prepare an integrated clinical and safety report. Prior to issuing the final CSR, [redacted] will prepare a draft report for approval by the Sponsor. The report will be in accordance with the ICH E3 Guideline for Industry: Structure and Content of CSRs. The draft report will be submitted for Quality Assurance audit, the findings of which will be incorporated into the final version.

An electronic copy of the final CSR will be made available to the Sponsor. The study report will be provided in PDF and MS Word formats unless agreed otherwise by [redacted] Reports requiring specialized Sponsor formats/alternative computer software packages may be possible on request from the Sponsor but may involve extra time and cost. Electronic datasets will also be provided to the Sponsor on issuance of the final report.

After review by the Sponsor, a final CSR will be submitted to the Sponsor which incorporates the Sponsor's comments.

14.2. CONFIDENTIALITY AND OWNERSHIP OF DATA, USE OF THE STUDY RESULTS AND PUBLICATION

All materials, information (oral or written), and unpublished documentation provided to the Investigators (or any company/institution acting on their behalf), including this protocol, the patient CRFs, and the Investigator's Brochure, are the exclusive property of the Sponsor and may not be published, given, or disclosed, either in part or in whole, by the Investigator or by any person under his/her authority to any third party without the prior express consent of the Sponsor.

However, the submission of this protocol and other necessary documentation to the ethics committee (IRB/IEC) and the Competent Authority is expressly permitted, their members having the same obligation of confidentiality.

The Investigator shall consider all information, results, discoveries, records (accumulated, acquired, or deduced) in the course of the study, other than that information to be disclosed by law, as confidential and shall not disclose any such results, discoveries, or records to any third party without the Sponsor's prior written consent.

The Sponsor retains exclusive ownership of all data, results, reports, findings, discoveries, and any other information collected during this study. Therefore, the Sponsor reserves the right to use the data from the present study, either in the form of Case Report Forms (or copies of these), or in the form of a report, with

or without comments and with or without analysis, in order to submit them to the Health Authorities of any country.

When the Sponsor generates reports for presentations to regulatory agencies, one or more of the Investigators who has/have contributed significantly to the study will be asked to endorse the final report. The endorsement is required by some regulatory agencies.

Furthermore, in the event that the study generates patentable results, the Investigator (or entity acting on his/her behalf according to local requirements) shall refrain from filing patent application(s) on such results, which will be filed by the Sponsor or its designees in its own name and at its expense.

Clinical study will be registered on the open access website http://www.clinicaltrials.gov before the screening of the first patient in the study.

It is the policy of the Sponsor to encourage the presentation and/or publication of the results of their studies, using only clean, checked, and validated data in order to ensure the accuracy of the results.

The publication of study results will be agreed between the Sponsor and the Investigators.

At least 45 days in advance of proposed submission, the Investigator should forward a copy of the manuscript or abstract for review by the Sponsor, and, if necessary, delay publication or communication for a limited time in order to protect the confidentiality or proprietary nature of any information contained therein. The Sponsor may also request that the Sponsor's name and/or names of one or several of its employees appear or not appear in such publication.

15. REFERENCES LIST

1. Day CP, James OF. Steatohepatitis: a tale of two "hits"? *Gastroenterology*. 1998;114:842-845.
2. Jou J, Choi SS, Diehl AM. Mechanisms of disease progression in nonalcoholic fatty liver disease. *Semin Liver Dis*. 2008;28: 370-379.
3. Edmison J, McCullough AJ. Pathogenesis of nonalcoholic steatohepatitis: human data. *Clin Liver Dis*. 2007;11:75-104.
4. Browning JD, Horton JD. Molecular mediators of hepatic steatosis and liver injury. *J Clin Invest*. 2004;114:147-152.
5. Ikejima K, Honda H, Yoshikawa M, et al. Leptin augments inflammatory and profibrogenic responses in the murine liver induced by hepatotoxic chemicals. *Hepatology*. 2001;34: 288-297.
6. Poniachik J, Santibanez C, Haim D, et al. Enhancement in liver nuclear factor-kb (NF-KB) and activator protein 1 (AP-1) DNA binding in obese patients with nonalcoholic fatty liver disease. The 43rd Annual Meeting of the European Association for the Study of the Liver. Milan, Italy, 2008.
7. Yamauchi T, Kamon J, Minokoshi Y, et al. Adiponectin stimulates glucose utilization and fatty-acid oxidation by activating AMP-activated protein kinase. *Nat Med*. 2002;8(11):1288-95. Epub 2002 Oct 7.
8. Targher G, Bertolini L, Rodella S, et al. Associations between plasma adiponectin concentrations and liver histology in patients with nonalcoholic fatty liver disease. *Clin Endocrinol (Oxf).* 2006;64:679-683.
9. Xu H, Barnes G, Yang Q, et al. Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance. *J Clin Invest*. 2003;112(12):1821-1830.
10. Pessayre D, Fromenty B, Mansouri A. Mitochondrial injury in steatohepatitis. *Eur J Gastroenterol Hepatol*. 2004;16:1095-1105.
11. Crespo J, Cayon A, Fernandez-Gil P, et al. Gene expression of tumor necrosis factor alpha and TNF-receptors, p55 and p75, in nonalcoholic steatohepatitis patients. *Hepatology*. 2001;34:1158–1163.
12. Hotamisligil GS, Arner P, Caro JF, et al. Increased adipose tissue expression of tumor necrosis factor-alpha in human obesity and insulin resistance. *J Clin Invest.* 1995;95:2409-2415.
13. Ramalho RM, Cortez-Pinto H, Castro RE, et al. Apoptosis and Bcl-2 expression in the livers of patients with steatohepatitis*. Eur J Gastroenterol Hepatol*. 2006;18:21-29.
14. Laurin J, Lindor KD, Crippin JS, et al. Ursodeoxycholic acid or clofibrate in the treatment of nonalcohol-induced steatohepatitis: a pilot study. *Hepatology*. 1996;23(6):1464-1467.
15. Shan W, Nicol CJ, Bility MT, et al. Peroxisome proliferator-activated receptor-beta/delta protects against chemically induced liver toxicity in mice, *Hepatology*. 2008;47(1):225-235.
16. Risérus U, Sprecher D, Johnson T, et al. Activation of peroxisome proliferator-activated receptor (PPAR) delta promotes reversal of multiple metabolic abnormalities, reduces oxidative

stress, and increases fatty acid oxidation in moderately obese men. *Diabetes*. 2008;57(2):332-339. Epub 2007 Nov 16.

17. Kang K, Reilly SM, Karabacak V, et al. Adipocyte-derived TH2 cytokines and myeloid PPAR delta regultate macrophage polarization and insulin sensitivity. *Cell Metab.* 2008;7:485-495.
18. Odegaard JI, Ricardo-Gonzalex RR, Red Eagle A et al. Alternative M2 activation of Kupffer cells by PPARδ ameliorates obesity induced insulin resistance. *Cell Metab*. 2008;7:496-507.
19. Cattley RC, Deluca j, Elcombe C, et al. Do peroxisome proliferating compounds pose a hepatocarcinogenic hazard to humans? *Regul Toxicol Pharmacol*. 2008;27(1 Pt 1):47-60.
20. Musso G, Gambino R, Cassader M, Pagano G . Meta-analysis: natural history of nonalcoholic fatty liver disease (NAFLD) and diagnostic accuracy of non-invasive tests for liver disease severity. *Ann Med*. 2011;43(8):617-649.
21. Ekstedt M, Franzen LE, Mathiesen UL, et al. Long-term follow-up of patients with NAFLD and elevated liver enzymes. *Hepatology.* 2006;44(4):865-873.
22. Angulo P, Kleiner DE, Dam-Larsen S, et al. Liver Fibrosis, but No Other Histologic Features, Is Associated With Long-term Outcomes of Patients With Nonalcoholic Fatty Liver Disease. *Gastroenterology.* 2015;149(2):389-397 e310.
23. Argo CK, Northup PG, Al-Osaimi AM, Caldwell SH . Systematic review of risk factors for fibrosis progression in nonalcoholic steatohepatitis. *J Hepatol*. 2009;51(2):371-379.
24. Pagadala MR, McCullough AJ. The relevance of liver histology to predicting clinically meaningful outcomes in nonalcoholic steatohepatitis. *Clin Liver Dis* 2012;16(3):487-504.
25. Singh S, Allen AM, Wang Z, Prokop LJ, Murad MH, Loomba R. Fibrosis progression in nonalcoholic fatty liver vs nonalcoholic steatohepatitis: a systematic review and meta-analysis of paired-biopsy studies. *Clin Gastroenterol Hepatol.* 2015;13(4):643-654.
26. Hashimoto E, Tokushige K. Prevalence, gender, ethnic variations, and progression of NASH. *J Gastroenterol.* 2011;46(supplement 1):63-69.
27. Younossi ZM, Stepanova M, Rafiq N, et al. Pathologic criteria for nonalcoholic steatohepatitis: interprotocol agreement and ability to predict liver-related mortality. *Hepatology.* 2011;53(6):1874-1882.
28. Ratziu V, de Ledinghen V, Oberti F, et al. A randomized controlled trial of high-dose ursodesoxycholic acid for nonalcoholic steatohepatitis. *J Hepatol.* 2011;54(5):1011-1019.
29. Sanyal AJ, Brunt EM, Kleiner DE, et al. Endpoints and clinical trial design for nonalcoholic steatohepatitis. *Hepatology*. 2011;54:344-353.
30. Sanyal AJ, Friedman SL, McCullough AJ, et al. Challenges and opportunities in drug and biomarker development for nonalcoholic steatohepatitis: findings and recommendations. *Hepatology.* 2015;61(4):1392-1405.
31. McPherson S, Hardy T, Henderson E, et al. Evidence of NAFLD progression from steatosis to fibrosing-steatohepatitis using paired biopsies: implications for prognosis and clinical management. *J Hepatol*. 2015;62(5):1148-1155.

32. Dunn W, Xu R, Wingard DL, et al. Suspected nonalcoholic fatty liver disease and mortality risk in a population-based cohort study. *Am J Gastroenterol.* 2008;103(9):2263-2271.
33. Rafiq N, Bai C, Fang Y, et al. Long-term follow-up of patients with nonalcoholic fatty liver. *Clin Gastroenterol Hepatol.* 2009;7(2):234-328.
34. Clinical Trial Facilitation Group (2014). Recommendations related to contraception and pregnancy testing in clinical trials. Available at: http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf
35. Neuschwander-Tetri BA, Loomba R, Sanyal AJ, et al. Farnesoid X nuclear receptor ligand obeticholic acid for non-cirrhotic, nonalcoholic steatohepatitis (FLINT): a multicentre, randomised, placebo-controlled trial. *Lancet*. 2015;385(9972):956-965.
36. Saville RS and Koch G. Estimating Covariate-Adjusted Log Hazard Ratios in Randomized Clinical Trials Using Cox Proportional Hazards Models and Nonparametric Randomization Based Analysis of Covariance. Journal of Biopharmaceutical Statistics. 2013 23: 477-490.
37. Zink RC and Koch G. NParCov3: A SAS/IML Macro for Nonparametric Randomization-Base Analysis of Covariance. Journal of Statistical Software. 2012 July 50:3.

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Appendices

APPENDIX I: WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

"The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by

individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

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19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and

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standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain

for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made

publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

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APPENDIX II: ADEQUATE DIET AND LIFESTYLE RECOMMENDATIONS

Essential Components of Therapeutic Lifestyle Changes (TLC)

Component	Recommendation
LDL-raising nutrients	
Saturated fats*	Less than 7% of total calories
Dietary cholesterol	Less than 200 mg/day
Therapeutic options for LDL lowering	
Plant stanols/sterols	2 grams per day
Increased viscous (soluble) fiber	10–25 grams per day
Total calories (energy)	Adjust total caloric intake to maintain desirable body weight/prevent weight gain
Physical activity	Include enough moderate exercise to expend at least 200 kcal per day

* *Trans* fatty acids are another LDL-raising fat that should be kept at a low intake.

Macronutrient Recommendations for the TLC Diet

Component	Recommendation
Polyunsaturated fat	Up to 10% of total calories
Monounsaturated fat	Up to 20% of total calories
Total fat	25–35% of total calories*
Carbohydrate†	50–60% of total calories*
Dietary fiber	20–30 grams per day
Protein	Approximately 15% of total calories

* ATP III allows an increase of total fat to 35 percent of total calories and a reduction in carbohydrate to 50 percent for persons with the metabolic syndrome. Any increase in fat intake should be in the form of either polyunsaturated or monounsaturated fat.
† Carbohydrate should derive predominantly from foods rich in complex carbohydrates including grains—especially whole grains—fruits, and vegetables.

APPENDIX III: PERMITTED/NON-PERMITTED MEDICATION

Table I: NON-PERMITTED MEDICATION AND CONDITION

Medications	**When**
Same pharmacological class (PPAR agonists)	
Thiazoledinediones (glitazones [pioglitazone and rosiglitazone])	From 6 months prior to diagnostic liver biopsy* up to end of study treatment (EOT) Visit
Fibrates	From 2 months prior to Randomization up to EOT Visit
Medication that may induce steatosis/steatohepatitis	
Corticosteroids (parenteral & oral chronic administration)	From 30 days prior to first Screening Visit up to EOT Visit
Amiodarone	
Tamoxifen	
Methotrexate	
Medication that may interact with absorption, metabolism, etc	
Indomethacin	From Randomization up to EOT Visit

* Given the potential effect on diagnostic liver biopsy of patients previously treated by glitazones

Table II: PERMITTED MEDICATION AND CONDITION

Medications	When
Antidiabetic therapy	
GLP-1 agonist	Dose stability required in the 6 months prior to the diagnostic liver biopsy No qualitative change (i.e., no initiation of a new drug) from at least 6 months prior to the diagnostic liver biopsy up to 72-week of treatment (V7). Dose changes after randomization should be avoided
All other ATD therapy (insulin, sulfonylureas, metformin, gliptins)	No qualitative change (i.e., no initiation of a new drug) from at least 6 months prior to the diagnostic liver biopsy and up to Randomization(Dose changes are allowed). Dose changes after randomization are allowed.
SGLT2-inhibitors	No qualitative change (i.e., no implementation of a new drug)from at least 6 months prior to the diagnostic liver biopsy up to 72-weeks of treatment (V7). Dose changes after randomization should be avoided.
Lipid lowering therapy	
Statins	Dose stability required from at least 2 months prior to Screening . Dose changes are allowed after Randomization if judged necessary by the physician
Ezetimibe	
Other nonfibrate lipid lowering therapies	
Others	
Vitamin E >400 IU/day	Dose stability required from at least 6 months prior to the diagnostic liver biopsy. Dose changes should be avoided up to EOT
PUFAs >2 g/day	
Ursodeoxycholic acid	

Abbreviations: ATD = autoimmune thyroid disease; EOT = end of study treatment; GLP-1 =glucagon-like peptide 1; PUFA = polyunsaturated fatty acids; SGLT2 = sodium/glucose cotransporter 2.

APPENDIX IV: ALCOHOL COMPARISON TABLE

Alcohol type	Alcohol by volume (ABV)	Volume		Amount of alcohol	
		Fluid ounce	mL	Units 2	grams
Beer	3.5%	12	350	0.7	9.8
Beer	5%	12	350	1	14
Cider	7%	12	350	1.4	19.6
Distilled spirits or liquor 1	40%	1.5	45	1	14
Wine	12%	5	150	1	14

1. e.g., gin, rum, vodka, whiskey.
2. Units calculated using the cleave Books calculator for units of drink, using the US definition of 1 unit of alcohol as 17.7 mL (14.0 g) of pure alcohol (http://www.cleavebooks.co.uk/scol/ccalcoh3.htm).

APPENDIX V: PRODUCT CARTON AND WALLET LABELING

	Carton	Wallet
Protocol number	X	X
Sponsor details	X	X
Site number	X	-
Subject ID	X	X
Kit number	X	X
Visit number	X	-
Lot number	X	X
Expiry date	X	X
Contents	X	X
Route of administration	X	X
Administration instructions	X	X
"For Clinical Trial Use only."	X	X
"Keep out of reach of Children."	X	X
Storage details	X	X
Instructions for product and package return at next visit	X	X

GENFIT
TOWARDS BETTER MEDICINE

CLINICAL PROTOCOL – PHASE 3

Protocol N° GFT505-315-1

EudraCT N°2015-005385-38

IND number: 115028

Amendment 3: Final 4.0– Release date 03 January 2020

Supersedes previous Version 3.0 - Release date: 03 April 2017

A Multicenter, Randomized, Double-Blind, Placebo-Controlled Phase III Study to Evaluate the Efficacy and Safety of Elafibranor in Patients with Nonalcoholic Steatohepatitis (NASH) and fibrosis

International Coordinating Investigator Committee	[redacted]	[redacted]
Sponsor	**GENFIT**	Parc Eurasanté 885, Avenue Eugène Avinée 59120 LOOS, France
Represented by:	[redacted]	[redacted]

CLINICAL STUDY PROTOCOL SIGNATURE PAGE

Protocol N°: **GFT505-315-1 / EudraCT N° 2015-005385-38/ IND n°115028**

Version number: **4.0**

Release date: **03 January 2020**

TITLE: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Phase III Study to Evaluate the Efficacy and Safety of Elafibranor in Patients with Nonalcoholic Steatohepatitis (NASH) and fibrosis.

In signing below, I give agreement to the protocol.
International Coordinators:

[redacted]

[redacted]

Signature

[redacted]

Date (dd-mmm-yyyy)

CLINICAL STUDY PROTOCOL SIGNATURE PAGE

Protocol N°: **GFT505-315-1 / EudraCT N° 2015-005385-38/ IND n°115028**

Version number: **4.0**

Release date: **03 January 2020**

TITLE: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Phase III Study to Evaluate the Efficacy and Safety of Elafibranor in Patients with Nonalcoholic Steatohepatitis (NASH) and fibrosis.

In signing below, I give agreement to the protocol.

[redacted]

[redacted]

[redacted]

Signature *Date (dd-mmm-yyyy)*

CLINICAL STUDY PROTOCOL SIGNATURE PAGE

Protocol N°: **GFT505-315-1 / EudraCT N° 2015-005385-38/ IND n°115028**

Version number: **4.0**

Release date: **03 January 2020**

TITLE: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Phase III Study to Evaluate the Efficacy and Safety of Elafibranor in Patients with Nonalcoholic Steatohepatitis (NASH) and fibrosis.

In signing below, I give agreement to the protocol.

[redacted]

[redacted]

Signature

[redacted]

Date (dd-mmm-yyyy)

CLINICAL STUDY PROTOCOL SIGNATURE PAGE

Protocol N°: **GFT505-315-1 / EudraCT N° 2015-005385-38/ IND n°115028**

Version number: **4.0**

Release date: **03 January 2020**

TITLE: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Phase III Study to Evaluate the Efficacy and Safety of Elafibranor in Patients with Nonalcoholic Steatohepatitis (NASH) and fibrosis.

In signing below, I give agreement to the protocol.

On behalf of (the Sponsor): GENFIT
Parc Eurasanté
885, Avenue Eugène Avinée
59120 LOOS – France

Name: [redacted]

[redacted]

Signature

[redacted]

Date (dd-mmm-yyyy)

CLINICAL STUDY PROTOCOL

INVESTIGATOR SIGNATURE PAGE

PROTOCOL TITLE: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Phase III Study to Evaluate the Efficacy and Safety of Elafibranor in Patients with Nonalcoholic Steatohepatitis (NASH) and fibrosis.

PROTOCOL NUMBER: GFT505-315-1

EudraCT Number: 2015-005385-38

IND Number: 115028

CLINICAL PHASE: III

VERSION: 4.0

DATE: 03 January 2020

SPONSOR: GENFIT,
Parc Eurasanté,
885 Avenue Eugène Avinée,
59120 LOOS - France

In signing below, I confirm having read the protocol, and give agreement to the protocol.

INVESTIGATOR NAME: _____

INSTITUTION NAME: _____

INSTITUTION ADDRESS: _____

_____

SIGNATURE: _____

DATE: _____ /_____ /_____

Day Month Year

STUDY CONTACTS

Protocol N°: **GFT505-315-1/ EudraCT N° 2015-005385-38/ IND n° 115028**

International Coordinating Investigator Committee	[redacted]	[redacted]
Sponsor	GENFIT	Parc Eurasanté 885, Avenue Eugène Avinée 59120 LOOS - France
[redacted]	[redacted]	[redacted]
CRO for monitoring, data management & statistics	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Pharmacovigilance	[redacted]	[redacted]

IXRS	[redacted]
Study drug supplier	[redacted]
Central laboratory	[redacted]
Central pathology laboratory	[redacted]
ePRO	[redacted]

AMENDMENT 3: 2020

Amendment 3 is a substantial change to address the addition of a key secondary objective at the surrogate endpoint analysis. Some metabolic endpoints (triglycerides, Non-HDL cholesterol, HDL cholesterol, LDL cholesterol, HbA1c [in diabetic patients], HOMA-IR [in non-diabetic patients]) are upgraded as key secondary endpoints that results in addition of a gatekeeping procedure to control the overall type I error rate at a two-sided alpha level of 0.01.
Furthermore, to be consistent with the Statistical Analysis Plan (SAP), some updates and clarifications are made in the "Statistical Methods and Data Analysis" section.
Other updates to clarify the FibroScan assessments and the rules of discontinuation related to the liver function monitoring were added. The summary of the safety data was also updated to reflect the update of the effective Investigator's Brochure with no changes to the benefit/risk assessment to the medicinal product.
Added text is **bolded**; deleted text is ~~struck through~~.

Summary of major changes to the protocol:

Section	**New Text**
Section 2	2 TRIAL OBJECTIVES **To assess the efficacy and safety of elafibranor as compared to placebo in adult NASH patients with fibrosis stage 2 or 3 (F2-F3), the primary and secondary objectives are as follows:**
Section 2.2	2.2 KEY SECONDARY OBJECTIVES – AT SURROGATE ENDPOINT ANALYSIS To assess histological changes after 72 weeks of treatment, at the time of surrogate endpoint analysis, on the following endpoint: • Percentage of patients with improvement of fibrosis of at least 1 stage according to NASH CRN scoring. **To assess the clinical benefit after 72 weeks of treatment on the following metabolic endpoints:** • **Changes from baseline in triglycerides, Non-HDL cholesterol, HDL cholesterol, LDL cholesterol, HbA1c (in diabetic patients), HOMA-IR (in non-diabetic patients)**

Section	**New Text**
Section 2.3	2.3 OTHER SECONDARY OBJECTIVES • **To assess histological changes after 72 weeks of treatment and at the end of the LTTP on the following endpoints:** ○ **percentage of patients with resolution of NASH without worsening of fibrosis (at the end of LTTP)** ○ **percentage of patients with improvement of fibrosis of at least 1 stage according to NASH CRN scoring (at the end of LTTP)** ○ **percentage of patients with improvement of fibrosis of at least 1 stage according to NASH CRN scoring without worsening of NASH** ○ **percentage of patients with no worsening of fibrosis and no worsening of NASH** ○ **percentage of patients with resolution of NASH and improvement of Fibrosis** ○ **percentage of patients with at least a 1 point improvement in histological scores (NASH CRN scoring: NAS [sum of steatosis, hepatic ballooning and lobular inflammation], steatosis, hepatic ballooning, lobular inflammation), fibrosis (NAFLD Ishak scoring system), or portal inflammation** ○ **percentage of patients with improvement of NAS of at least 2 points** ○ **percentage of patients with improvement of NAS of at least 2 points and with at least 1 point improvement in hepatic ballooning** ○ **percentage of patients with at least a 1 point improvement in disease activity score (sum of ballooning and lobular inflammation scores) according to NAS scoring and steatosis-activity-fibrosis (SAF) scoring** ○ **percentage of patients with at least a 1 point improvement in disease activity score (sum of ballooning and lobular inflammation scores) according to NAS scoring and with at least 1 point improvement in hepatic ballooning**

Section	**New Text**
	○ **percentage of patients with at least a 1 point improvement in disease activity score (sum of ballooning and lobular inflammation scores) according to steatosis-activity-fibrosis (SAF) scoring and with at least 1 point improvement in hepatic ballooning** ○ **percentage of patients with at least 2 points improvement in disease activity score according to NAS scoring and SAF scoring** ○ **changes in NAS, fibrosis (using NASH CRN and NAFLD Ishak scoring system), steatosis, hepatic ballooning, lobular inflammation, portal inflammation, SAF activity score** ○ **changes in area of fibrosis (normalized Collagen Proportional area in %) by morphometry** • ~~To assess histological changes after 72 weeks of treatment and follow-up biopsy on the following endpoints:~~ ○ ~~percentage of patients with resolution of NASH without worsening of fibrosis (follow-up biopsy)~~ ○ ~~percentage of patients with improvement of fibrosis of at least 1 stage according to NASH CRN scoring~~ ○ ~~percentage of patients with at least 1 point improvement in histological scores (NASH CRN scoring: total NAS, steatosis, hepatic ballooning, lobular inflammation), fibrosis (NAFLD Ishak scoring system), or portal inflammation~~ ○ ~~percentage of patients with improvement of NAS of at least 2 points~~ ○ ~~percentage of patients with at least a 1 point improvement in steatosis activity fibrosis (SAF) activity score~~ ○ ~~mean changes in NAS, steatosis, hepatic ballooning, lobular inflammation, portal inflammation, SAF activity score~~ ○ ~~changes in area of fibrosis by morphometry~~ ○ ~~mean changes in fibrosis using NASH CRN and NAFLD Ishak scoring~~. • To assess the following endpoints at Week 72 and at the end of the LTTP: ○ changes in liver enzymes and liver markers ○ changes in noninvasive markers of fibrosis and steatosis ○ changes in lipid parameters ○ variation in body weight

Section	**New Text**
	○ changes in insulin resistance and glucose homeostasis markers ○ changes in inflammatory markers ○ changes in cardiovascular risk profile as assessed by Framingham scores ○ **changes in liver stiffness by Fibroscan measurement** ○ changes in quality of life (36-Item Short-Form Health Survey [SF-36]~~)~~ questionnaire). ○ To assess the onset to:**histological** liver cirrhosis ○ death of any cause ○ any portal hypertension or cirrhosis related events ○ cardiovascular events ○ liver-related death events
Section 2.5	2.5 EXPLORATORY OBJECTIVES FOR F1 GROUP **AND THE OVERALL POPULATION (WHATEVER THE FIBROSIS STAGE – F1, F2 OR F3)** • To explore~~ the following endpoints ,~~ in F1 patients **and** in the **overall population whatever the fibrosis stage (F1, F2 or F3), the same endpoints as for the primary and secondary objectives.**~~exploratory group at Week 72 and at the end of the LTTP:~~ ○ ~~resolution of NASH without worsening of fibrosis~~ ○ ~~percentage of patients with at least 1 point reduction in NASH CRN fibrosis score and NAFLD Ishak score~~ ○ ~~percentage of patients with at least 1 point improvement in NAS, steatosis, ballooning, lobular inflammation, or portal inflammation~~ ○ ~~percentage of patients with improvement of NAS of at least 2 points~~ ○ ~~percentage of patients with at least a 1 point improvement in SAF activity score~~ ○ ~~mean changes in NAS, fibrosis (using NASH CRN or NAFLD Ishak scoring system), steatosis, hepatic ballooning, lobular inflammation, portal inflammation, and SAF activity score.~~

Section	**New Text**
	○ ~~changes in area of fibrosis by morphometry.~~ • ~~To explore~~ ~~the~~ ~~following endpoints in F1 patients at Week 72 and after the LTTP:~~ ○ ~~composite endpoint~~ as ~~described in Section 2.1.2.~~ ○ ~~cardiovascular events~~ ○ ~~changes in liver enzymes and liver markers~~ ○ ~~changes in noninvasive markers of fibrosis and steatosis~~ ○ ~~changes in lipid parameters~~ ○ ~~variation in body weight~~ ○ ~~changes in insulin resistance and glucose homeostasis markers~~ ○ ~~changes in inflammatory markers~~ ○ ~~changes in cardiovascular risk profile as assessed by Framingham scores~~ ○ ~~changes in quality of life (SF-36 questionnaire)~~ • ~~To assess the tolerability and safety.~~
Section 9.2.1	9.2.1 Surrogate endpoint – resolution of NASH The first surrogate endpoint for this study is resolution of NASH without worsening of fibrosis after 72 weeks of treatment. Resolution of NASH is defined as the disappearance of ballooning (i.e., grade 0) and disappearance or persistence of minimal lobular inflammation (i.e., grade 0 or 1) with an overall pattern of injury not qualifying for steatohepatitis. Worsening of fibrosis is evaluated using NASH CRN fibrosis staging system and defined as progression of at least 1 stage. This surrogate endpoint will be formally assessed at the time of the surrogate efficacy analysis when at least **the first** 1023 ~~of~~ ~~the~~**randomized** F2 ~~to~~**and** F3 patients complete the 72 week treatment period or discontinue early from the study **treatment** (see Section 9.8.1 for details). An additional exploratory analysis of this endpoint will take place at the time of the final analysis.

Section	**New Text**
Section 9.2.3	9.2.3 Key Secondary Endpoints The key secondary ~~endpoint is~~**endpoints are**: • Percentage of patients with improvement of fibrosis of at least 1 stage according to NASH CRN scoring at 72 weeks. ~~This~~**To assess the clinical benefit after 72 weeks of treatment on the following metabolic endpoints:** • **Changes from baseline to Week 72 in triglycerides, Non-HDL cholesterol, HDL cholesterol, LDL cholesterol, HbA1c (in diabetic patients), HOMA-IR (in non-diabetic patients)** **These** key secondary endpoint**s** will be assessed at the time of the surrogate endpoint analysis (at least **the first** 1023 **randomized** patients with fibrosis stage F2 and F3) for the resolution of NASH without worsening of fibrosis endpoint.
Section 9.2.4	9.2.4 Other Secondary Endpoints The other secondary endpoints are: • To assess histological changes after 72 weeks of treatment and ~~follow up biopsy~~**at the end of the LTTP** on the following endpoints: o percentage of patients with resolution of NASH without worsening of fibrosis (~~follow up biopsy~~**at the end of LTTP**) o percentage of patients with improvement of fibrosis of at least 1 stage according to NASH CRN scoring **(at the end of LTTP)** o percentage of patients with ~~at least 1 point~~ improvement ~~in~~ **of fibrosis of at least 1 stage according to NASH CRN scoring without worsening of NASH** o **percentage of patients with no worsening of Fibrosis and no worsening of NASH** o **percentage of patients with resolution of NASH and improvement of Fibrosis**

Section	**New Text**
	○ **percentage of patients with at least a 1 point improvement in** histological scores (NASH CRN scoring: ~~total~~ NAS~~,~~ **[sum of steatosis, hepatic ballooning and lobular inflammation],** steatosis, hepatic ballooning, lobular inflammation), fibrosis (NAFLD Ishak scoring system), or portal inflammation ○ percentage of patients **with** improvement of NAS of at least 2 points ○ **percentage of patients with improvement of NAS of at least 2 points and with at least 1 point improvement in hepatic ballooning** ○ percentage of patients with at least a 1 point improvement in ~~SAF~~**disease** activity score **(sum of ballooning and lobular inflammation scores) according to NAS scoring and steatosis-activity-fibrosis (SAF) scoring** ○ ~~mean~~ **percentage of patients with at least a 1 point improvement in disease activity score (sum of ballooning and lobular inflammation scores) according to NAS scoring and with at least 1 point improvement in hepatic ballooning** ○ **percentage of patients with at least a 1 point improvement in disease activity score (sum of ballooning and lobular inflammation scores) according to steatosis-activity-fibrosis (SAF) scoring and with at least 1 point improvement in hepatic ballooning** ○ **percentage of patients with at least 2 points improvement in disease activity score according to NAS scoring and SAF scoring** ○ changes in NAS, **fibrosis (using NASH CRN and NAFLD Ishak scoring system),** steatosis, hepatic ballooning, lobular inflammation, portal inflammation~~,~~ **and** SAF activity score ○ changes in area of fibrosis **(normalized Collagen Proportional area in %)** by morphometry**.** ~~○ mean changes in fibrosis using NASH CRN and NAFLD Ishak scoring.~~ • To assess the following endpoints at Week 72 and at the end of the LTTP: ○ changes in liver enzymes and liver markers ○ changes in noninvasive markers of fibrosis and steatosis ○ changes in lipid parameters ○ variation in body weight ○ changes in insulin resistance and glucose homeostasis markers ○ changes in inflammatory markers ○ changes in cardiovascular risk profile as assessed by Framingham scores ○ **changes in liver stiffness by Fibroscan measurement** ○ changes in quality of life (SF-36 questionnaire). • To assess the onset to:

Section	**New Text**
	○ **histological** liver cirrhosis ○ death of any cause ○ any portal hypertension or cirrhosis related events ○ cardiovascular events ○ liver-related death events.
Section 9.3	9.3 Analysis Sets The following analysis sets will be used in this study: •Enrolled: all patients who sign informed consent. This set will be used to summarize disposition. •ITT: all randomized F2 and F3 patients. This set will be used to summarize efficacy. The main analysis of the primary and key secondary endpoints will be based on the ITT. •Safety set (SS): all ~~randomized~~ F2 and F3 patients who receive at least 1 dose of study drug. This set will be used to summarize safety. •**Efficacy evaluable set (EES): All F2 and F3 patients in the ITT population who have taken at least one dose of study treatment and have a reliable liver biopsy at both baseline and at the end of the 72 week treatment period.** •Per protocol set (PPS): all F2 and F3 patients who receive at least 1 dose of study drug and do not have any important protocol deviations leading to exclusion from the PPS. Important protocol deviations will be defined in the SAP and agreed prior to database lock. Supportive analysis of the primary and key secondary endpoints will be based on the PPS.

Section	**New Text**
	•Exploratory F1 cohort: All randomized F1 patients who have taken at least 1 dose of study drug. •Full Intent-To-Treat Set (FITT): all randomized patients. •Full Safety Set (FSS): all ~~randomized~~ patients who receive at least 1 dose of study drug. Patients in the ITT, FITT, **EES**, PPS, and exploratory F1 cohorts (study population and efficacy data) will **be** analyzed based on randomized treatment. Patients in the SS, FSS, and exploratory F1 cohorts (safety data) will be analyzed based on actual treatment received.
Section 9.4.1	9.4.1 Resolution of NASH The number and percentage of patients with resolution of NASH without worsening of fibrosis at the end of the 72 week treatment period will be summarized by treatment group. The main analysis will be performed using a logistic regression model, with fixed terms for treatment, type 2 diabetes (yes, no), gender (male, female), fibrosis stage (F2, F3) and baseline NAS. ~~The~~ **According to the method described in Ge et al. (2011), the** statistical model will be used to ~~calculate~~**estimate** the ~~odds ratio~~**difference** (elafibranor/placebo) **in rate of resolution of NASH without worsening of fibrosis** and **its** 99% ~~confidence interval.~~**CI.** The main confirmatory analysis will be performed when at least **the first** 1023 **randomized** F2/F3 patients have completed the 72 week treatment period or discontinued from the study **treatment**. The main analysis will be based on the ITT. Supportive analysis will be based on the **EES and** PPS. Patients with missing data for resolution of NASH without worsening of fibrosis will be treated as a nonresponder for the main analysis. ~~Additional sensitivity analysis~~**Supplementary analyses** using multiple imputations and a pattern mixture model will be performed**, as well as sensitivity analysis using a Cochran-Mantel-Haenszel test**. Further details will be provided in the SAP.

Section	**New Text**
Section 9.5.1	9.5.1 Key secondary endpoint The number and percentage of patients with improvement of fibrosis according to NASH CRN scoring at the end of the 72 week treatment period will be summarized separately by treatment group. The data will be analyzed using a logistic regression model, with fixed terms for treatment, type 2 diabetes, gender, fibrosis stage and baseline NAS by NASH CRN scoring. The analysis will be performed at the time of the surrogate endpoint analysis when at least **the first** 1023 ~~of~~**randomized** patients with fibrosis stage F2 and F3 have completed the 72 week treatment period or discontinued from the study **treatment**. The null hypothesis will be tested at the two-sided 0.01 alpha level. **The key secondary efficacy endpoints will be tested only if the primary surrogate endpoint is statistically significant. A gatekeeping procedure will be constructed to control the overall Type I error rate for testing the key secondary efficacy endpoints at an overall two-sided alpha level of 0.01.** The main analysis will be based on the IIT. Supportive analyses will be based on the **EES and** PPS.
Section 9.5.2	9.5.2 Other secondary endpoints Time to event endpoints **such as time to first cardiovascular event/death** will be analyzed using the Cox proportional hazard's model in the same manner as time to clinical event/death. Continuous endpoints will be analyzed using a~~n~~ **repeated measures** Analysis of Covariance (ANCOVA) model with fixed terms for treatment, type 2 diabetes, gender, fibrosis stage, ~~and~~ baseline NAS, **and time-point and treatment by time-point interaction**. A~~n unstructured~~ **compound symmetry** covariance matrix will be used for this analysis. The statistical model will be used to calculate the mean treatment difference and 95% confidence interval. If the data does not meet the required assumptions for parametric tests, the data will be analyzed using a nonparametric analysis of covariance method of Zink and Koch[41].

Section	**New Text**
Section 9.5.3	9.5.3 Subgroup analyses Exploratory analyses of the primary and key secondary endpoints will be done for selected subgroups, including, but not limited to, the following: • Presence of type 2 diabetes (yes, no) • Gender (male, female) • Fibrosis (F2, F3) • Geographic region (North America, Europe, South America, Rest of World) • Race (Caucasian, Other) • Ethnicity (Hispanic, not Hispanic) • Age (<60, ≥60 years). • **PNPLA3 (absence or presence of risk allele G [i.e. CC vs GG/CG], and within the at risk group, homozygous vs. heterozygous for the risk allel G [i.e. CG vs GG])** • **Patients under statins (yes/no), defined as patients who have duration of IP exposure greater or equal to 60 days, with extent of exposure to statin greater than or equal to 30 days before the visit 7 biopsy date.**
Section 9.6	9.6 STRATEGIES TO CONTROL TYPE I ERROR ~~A hierarchical gate keeping strategy will be used to control for multiplicity for the~~ **The** key secondary ~~endpoint. If the resolution of NASH without worsening of fibrosis~~**efficacy endpoints will be tested only if the primary surrogate** endpoint is statistically significant~~,~~ **at a two-sided 1% significance level. A gatekeeping procedure will be constructed to control the overall Type I error rate for testing** the key secondary ~~endpoint, improvement~~**efficacy endpoints at an overall two-sided alpha level** of ~~fibrosis according to NASH CRN scoring,~~**0.01.**

Section	**New Text**
	The gatekeeping procedure will be ~~t~~**d**~~est~~**ail**ed in ~~a confirmatory manner~~**the SAP and set up using the general method for building multi-stage parallel gatekeeping procedures in multiplicity problems** with ~~a two sided α=0.01.~~**several families of null hypotheses (Dmitrienko and Tamhane, 2011, 2013).**
Section 9.7.2	9.7.2 Time to clinical event/death There is no long-term randomized clinical trial in a NASH population with moderate and severe liver fibrosis. In the 72-week FLINT trial, the total drop-out rate was 6.7%.[35] Therefore, we estimate an approximate annual drop-out rate of 4%. Based on these assumptions, 456 events are required to provide 80% power to show that elafibranor is superior to placebo with respect to time to clinical event/death. In order to obtain 456 events, at least 2022 patients will be required in the IIT. **The number of patients to be enrolled may be adjusted during the course of the study in a blinded manner to achieve the desired number of primary events. This will be accomplished using standard event forecasting methods (Anisimov, 2011).**
Section 9.8.1	9.8.1 Surrogate endpoint analysis The analysis of resolution of NASH without worsening of fibrosis will occur when **at least the first** 1023 randomized F2 and F3 patients complete 72 weeks of treatment or discontinue early from the study treatment. The null hypothesis will be tested at the two-sided 0.01 alpha level. At this time, a snapshot of the database will be cleaned and locked for analysis and potential Subpart H or conditional approval submission. This analysis will be done by an unblinded team separate from the study team; the study team will not be unblinded until the final analysis at the end of follow-up. **A Data integrity plan will be set-up to detail the blinding process and address how data will be published in view of marketing authorization and how integrity of the trial will be protected.**

Section	**New Text**
	The DSMB will also periodically review safety data from the study to ensure the well-being of study participants. ~~These safety reviews will be based on reports generated by the SAC and may~~ **One dedicated meeting will be held upon availability of the surrogate endpoint analysis results and DSMB will be provided with data summaries that will include** select**ed** efficacy results so that the DSMB can assess the likely benefit-risk profile of elafibranor. These are not considered a formal interim analysis, and no type I error adjustments will be done for these reviews. Details will be in the DSMB Charter.

Summary of minor changes to the protocol:

The following minor changes were made to the protocol. The changes do not impact the reliability of the data generated in the clinical trial or the safety or rights of the subjects:

- Study contact details have been updated for one of the Steering Committee members, for the sponsor representative, and several vendors representatives
- The version number and date were updated throughout the protocol
- The list of abbreviations has been updated
- Sections "Number of estimated randomized F2-F3 Patients" and "Study Duration (planned)" of the synopsis were updated. Appropriate sections of the core protocol were also updated to reflect the changes.
- The "Section 1.5 - Clinical Studies" was updated to issue synthetic Clinical Studies summaries reflecting the updates of the effective version of the Investigator's Brochure.
- The "Section 1.6 - Conclusion " was updated to reflect the updates of the effective version of the Investigator's Brochure.
- The "Section 6.2.5 - Fibroscan" was clarified for the assessment conditions.
- The "Section 6.3.2.1 - Monitoring of patients with normal baseline aminotransferase values" and the "Section 6.3.2.2 - Monitoring of patients with increased baseline aminotransferase values" were updated to clarify the conditions of the associated parameters "INR" and "eosinophilia".
- The "Section 6.3.3 - Threshold for diagnosis of cirrhosis" was updated for liver biopsy consideration

- The "Section 6.6 - Guidances for Investigators" was updated to reflect the updates of the effective version of the Investigator's Brochure.
- The section 7.4 has been very slightly clarified
- The section 9.5.4 has been updated to include the FITT

CLINICAL TRIAL SYNOPSIS

Sponsor:	Study Drug:	Protocol Number:
GENFIT	Elafibranor (GFT505): Propanoic acid, 2-[2,6-dimethyl-4-[3-[4-(methylthio)phenyl]-3-oxo-1(E)-propenyl] phenoxy]-2-methylpropanoic acid	GFT505-315-1

Title of the study:
A Multicenter, Randomized, Double-Blind, Placebo-Controlled Phase III Study to Evaluate the Efficacy and Safety of Elafibranor in Patients with Nonalcoholic Steatohepatitis (NASH) and fibrosis

Phase:
Phase III
Indication:
NASH

Study design and dose levels:
Randomized, double-blind, parallel groups (placebo or elafibranor [GFT505]) placebo-controlled study, evaluating the efficacy and safety of elafibranor 120 mg QD versus placebo in an adult NASH population with fibrosis. The first double-blind 72-week treatment period will assess the efficacy and safety of elafibranor on the resolution of NASH without worsening of fibrosis at the surrogate endpoint efficacy analysis, followed by a Long-term Treatment Period (LTTP) to assess efficacy on progression to cirrhosis, all-cause mortality, and liver-related clinical outcomes as measured by the onset of any of the listed adjudicated events.
Dose level
120 mg
Route of administration:
Oral (1 tablet once daily [QD])

To assess the efficacy and safety of elafibranor as compared to placebo in adult NASH patients with fibrosis stage 2 or 3 (F2-F3), the primary and secondary objectives are as follows:

Primary objective – surrogate endpoint analysis
To evaluate the efficacy of elafibranor 120 mg QD for 72 weeks versus placebo on resolution of NASH without worsening of fibrosis.

- Resolution of NASH is defined as the disappearance of ballooning and disappearance or persistence of minimal lobular inflammation (grade 0 or 1) with an overall pattern of injury not qualifying for steatohepatitis.
- Worsening of fibrosis is evaluated using the NASH Clinical Research Network (CRN) fibrosis staging system and defined as progression of at least 1 stage.

Primary objectives – long-term endpoints
To evaluate the efficacy of elafibranor 120 mg QD versus placebo on clinical outcomes described as a composite endpoint composed of death due to any cause, histological liver cirrhosis, and the full list of portal hypertension/cirrhosis related events:

- Liver transplantation
- MELD score ≥15
- Hepatocellular carcinoma
- the onset of:
    - variceal bleed,
    - hepatic encephalopathy,
    - spontaneous bacterial peritonitis,
    - ascites,
    - hepatorenal syndrome,
    - hepatopulmonary syndrome,
    - chronic gastrointestinal blood loss due to portal hypertensive gastropathy (provided that these lead to hospitalization or transfusion).

Key secondary objectives (at surrogate endpoint analysis)
To assess histological changes after 72 weeks of treatment on the following endpoint:

- Percentage of patients with improvement of fibrosis of at least 1 stage according to NASH CRN scoring.

To assess the clinical benefit after 72 weeks of treatment on the following metabolic endpoints:

- Changes from baseline in triglycerides, Non-HDL cholesterol, HDL cholesterol, LDL cholesterol, HbA1c (in diabetic patients), HOMA-IR (in non-diabetic patients)

Other secondary objectives

- To assess histological changes after 72 weeks of treatment and at the end of the LTTP on the following endpoints:
  - percentage of patients with resolution of NASH without worsening of fibrosis (at the end of LTTP)
  - percentage of patients with improvement of fibrosis of at least 1 stage according to NASH CRN scoring (at the end of LTTP)
  - percentage of patients with improvement of fibrosis of at least 1 stage according to NASH CRN scoring without worsening of NASH
  - percentage of patients with no worsening of Fibrosis and no worsening of NASH
  - percentage of patients with resolution of NASH and improvement of Fibrosis
  - percentage of patients with at least a 1 point improvement in histological scores (NASH CRN scoring: NAS [sum of steatosis, hepatic ballooning and lobular inflammation], steatosis, hepatic ballooning, lobular inflammation), fibrosis (NAFLD Ishak scoring system), or portal inflammation
  - percentage of patients with improvement of NAS of at least 2 points
  - percentage of patients with improvement of NAS of at least 2 points and with at least 1 point improvement in hepatic ballooning
  - percentage of patients with at least a 1 point improvement in disease activity score (sum of ballooning and lobular inflammation scores) according to NAS scoring and steatosis-activity-fibrosis (SAF) scoring
  - percentage of patients with at least a 1 point improvement in disease activity score (sum of ballooning and lobular inflammation scores) according to NAS scoring and with at least 1 point improvement in hepatic ballooning
  - percentage of patients with at least a 1 point improvement in disease activity score (sum of ballooning and lobular inflammation scores) according to steatosis-activity-fibrosis (SAF) scoring and with at least 1 point improvement in hepatic ballooning
  - percentage of patients with at least 2 points improvement in disease activity score according to NAS scoring and SAF scoring
  - changes in NAS, fibrosis (using NASH CRN and NAFLD Ishak scoring system), steatosis, hepatic ballooning, lobular inflammation, portal inflammation and SAF activity score
  - changes in area of fibrosis (normalized Collagen Proportional area in %) by morphometry
- To assess the following endpoints at Week 72, and at the end of the LTTP:
  - changes in liver enzymes and liver markers
  - changes in noninvasive markers of fibrosis and steatosis
  - changes in lipid parameters
  - variation in body weight
  - changes in insulin resistance and glucose homeostasis markers
  - changes in inflammatory markers
  - changes in cardiovascular risk profile as assessed by Framingham scores
  - changes in liver stiffness by Fibroscan measurement
  - changes in quality of life (36-Item Short-Form Health Survey [SF-36] questionnaire)
- To assess the onset to:
  - histological liver cirrhosis
  - death of any cause
  - any portal hypertension or cirrhosis related events
  - cardiovascular events
  - liver-related death events.

Exploratory objectives

- To constitute a biobank for discovery and validation of biomarkers in NASH.

Exploratory objectives for F1 group and the overall population (whatever the fibrosis stage – F1, F2 or F3)

- To explore, in F1 patients and in the overall population whatever the fibrosis stage (F1, F2 or F3), the same endpoints as for the primary and secondary objectives

Safety secondary objectives

- To assess the tolerability and safety of once a day administration of oral doses of elafibranor 120 mg:
  - serious adverse events, adverse events, physical examination, vital signs, medical history, electrocardiogram
  - hematological parameters
  - liver markers
  - renal biomarkers (including urinalysis)
  - cardiac biomarkers
  - metabolic parameters
  - other biochemical safety markers.

Patient population:

NASH diagnosed as:

Steatohepatitis evaluated by a centrally-read liver biopsy taken within 6 months prior to Screening (if no historical biopsy is available for NASH diagnosis, a liver biopsy will be performed during the Screening Period) with:

- At least a score of 1 in each component of the NAS (steatosis scored 0-3, ballooning degeneration scored 0-2, and lobular inflammation scored 0-3).
- NAS ≥4.
- fibrosis stage of 1 or greater and below 4, according to the NASH CRN fibrosis staging system.
  For patients with fibrosis stage 1, only patients at high risk of progression will be included, meaning with a NAS ≥5 and at least 2 of the following conditions: persistent elevated alanine aminotransferase (ALT; absence of normal value of ALT within the past year), obesity defined by a body mass index (BMI) ≥30, metabolic syndrome (NCEP ATP III definition), type 2 diabetes, or homeostasis model assessment of insulin resistance (HOMA-IR) >6.

At the end of the 72-week treatment period, patients will continue in the double-blind LTTP. Patients will be monitored by notably measuring the potential appearance of cirrhosis (based on FibroScan measurement for presence of cirrhosis associated with biological and clinical assessments). If histological cirrhosis is confirmed as well as any other event listed in the long-term composite endpoint, patients will be discontinued from study.

Number of estimated randomized F2-F3 Patients: at least 2022 patients (ratio 2:1)

- 674 patients in placebo group
- 1348 patients in elafibranor (GFT505) group

An additional 202 (10% of the F2-F3 patients) F1 patients at high risk of progression will be included as an exploratory arm.

Number of participating centers (planned): ~270 centers

Number of participating countries: 24 (Belgium, France, Germany, Italy, the Netherlands, Romania, Spain, UK, Switzerland, Portugal, Denmark, Finland, Sweden, Czech Republic, Russia, Turkey, USA, Canada, Mexico, Colombia, Argentina, Chile, Australia, South Africa)

Study duration per patient:

Estimated duration approximately 96 months, based on 456 patients experiencing a long-term composite endpoint event.

Schedule:

- Screening Period: Week -12 to Week -1 prior to Randomization.
- First Treatment Period: Week 0 to Week 72: period of treatment with elafibranor (GFT505) or placebo for 72 weeks.
- Long-term Treatment Period: Week 72 to end of study: extension of treatment with elafibranor (GFT505) or placebo (until occurrence of prespecified number of events).

Inclusion criteria:

Patients must meet all of the following inclusion criteria to be eligible for enrollment in the trial:

1. Males or females aged from 18 to 75 years inclusive at first Screening Visit.
2. Must provide signed written informed consent and agree to comply with the study protocol.
3. Females participating in this study must be of nonchildbearing potential or using highly efficient contraception for the full duration of the study and for 1 month after the end of treatment, as described below:

- Cessation of menses for at least 12 months due to ovarian failure,
- Surgical sterilization such as bilateral oopherectomy, hysterectomy, or medically documented ovarian failure
- If requested by local IRB regulations and/or National laws, sexual abstinence may be considered adequate (the reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient)
- Using a highly effective nonhormonal method of contraception (bilateral tubal occlusion, vasectomized partner, or intra-uterine device)
- Double contraception with barrier AND highly effective hormonal method of contraception (oral, intravaginal, or transdermal combined estrogen and progestogen hormonal contraception associated with inhibition of ovulation; oral, injectable, or implantable progestogen-only hormonal contraception associated with inhibition of ovulation; or intrauterine hormone-releasing system). The hormonal contraception must be started at least 1 month prior to Randomization.

4. Histological confirmation of steatohepatitis on a diagnostic liver biopsy by central reading of the slides (biopsy obtained within 6 months prior to Screening or during the Screening Period) with at least 1 in each component of the NAS (steatosis scored 0-3, ballooning degeneration scored 0-2, and lobular inflammation scored 0-3).
5. NAS ≥4.
6. Fibrosis stage of 1 or greater and below 4, according to the NASH CRN fibrosis staging system.
   For patients with fibrosis stage 1, only patients at high risk of progression will be included meaning with a NAS ≥5 and at least 2 of the following conditions: persistent elevated ALT (absence of normal value of ALT within the past year), obesity defined by a BMI ≥30, metabolic syndrome (NCEP ATP III definition), type 2 diabetes, or HOMA-IR >6.
7. Patients in whom it is safe and practical to proceed with a liver biopsy, and who agree to have:
   - 1 liver biopsy during the Screening Period for diagnostic purpose (if no historical biopsy within 6 months before Screening is available)
   - 1 liver biopsy after 72-weeks of treatment for assessment of the treatment effects on NASH
   - a final liver biopsy after approximately 4 years of treatment (V13), unless a liver biopsy has already been performed within the past year
   - 1 liver biopsy performed only in the case of suspicion of cirrhosis (to have a histological confirmation).
8. If a patient is treated with 1 of the following drugs: vitamin E (>400 IU/day), polyunsaturated fatty acids (>2 g/day), or ursodeoxycholic acid; a stable dose from at least 6 months prior to diagnostic liver biopsy is required.
9. For patients with type 2 diabetes, glycemia must be controlled. If glycemia is controlled by antidiabetic drugs, change in anti-diabetic therapy must follow these requirements:
   - no qualitative change 6 months prior to diagnostic liver biopsy up to Randomization (i.e., implementation of a new anti-diabetic therapy) for patients treated with metformin, gliptins, sulfonylureas, sodium/glucose cotransporter (SGLT) 2 inhibitors, glucagon-like peptide (GLP)-1 agonists, or insulin. Dose changes of these medications are allowed in the 6 months prior to diagnostic liver biopsy, except for GLP-1 agonists, which must remain on stable dose in the 6 months prior to diagnostic liver biopsy.
   - no implementation of GLP-1 agonists and SGLT2 inhibitors up to 72 weeks of treatment (V7).

   Initiation of any other antidiabetic drugs is allowed after Randomization based on treating physicians' judgment, except for glitazones which are prohibited 6 months prior to diagnostic liver biopsy until the end of treatment.

Exclusion criteria:

Patients who meet any of the following criteria will be excluded from entering the study:

1. Known chronic heart failure (Grade I to IV of New York Heart Association classification).
2. History of efficient bariatric surgery within 5 years prior to Screening, or planned bariatric surgery in the course of the study.
3. Uncontrolled hypertension during the Screening Period despite optimal antihypertensive therapy.
4. Type 1 diabetes patients.
5. Patients with hemoglobin A1c [HbA1c] >9.0%. If abnormal at the first Screening Visit, the HbA1c measurement can be repeated at the latest 2 weeks prior to Randomization. A repeated abnormal HbA1c (HbA1c >9.0%) leads to exclusion.
6. Patients receiving thiazoledinediones (glitazones [pioglitazone, rosiglitazone]) unless the drug was discontinued at least 6 months before the diagnostic liver biopsy.

7. Patients with a history of clinically significant acute cardiac event within 6 months prior to Screening such as: stroke, transient ischemic attack, or coronary heart disease (angina pectoris, myocardial infarction, revascularization procedures).
8. Weight loss of more than 5% within 6 months prior to Randomization.
9. Compensated and decompensated cirrhosis (clinical and/or histological evidence of cirrhosis). Notably, NASH patients with fibrosis stage = 4 according to the NASH CRN fibrosis staging system are excluded.
10. Current or recent history (<5 years) of significant alcohol consumption. For men, significant consumption is typically defined as higher than 30 g pure alcohol per day. For women, it is typically defined as higher than 20 g pure alcohol per day.
11. Pregnant or lactating females or females planning to become pregnant during the study period.
12. Other well documented causes of chronic liver disease according to standard diagnostic procedures including, but not restricted to:
    - positive hepatitis B surface antigen
    - positive hepatitis C Virus (HCV) RNA (tested for in case of known cured HCV infection or positive HCV Ab at Screening)
    - suspicion of drug-induced liver disease
    - alcoholic liver disease
    - autoimmune hepatitis
    - Wilson's disease
    - primary biliary cirrhosis, primary sclerosing cholangitis
    - genetic homozygous hemochromatosis
    - known or suspected hepatocellular carcinoma (HCC)
    - history or planned liver transplant, or current MELD score >12
13. Where applicable, patients not covered by Health Insurance System and/or not in compliance with the recommendations of National Law in force applicable to clinical trials.
14. Patients who cannot be contacted in case of emergency.
15. Known hypersensitivity to the investigation product or any of its formulation excipients.
16. Patients with previous exposure to elafibranor.
17. Patients who are currently participating in, plan to participate in, or have participated in an investigational drug trial or medical device trial containing active substance within 30 days or five half-lives, whichever is longer, prior to Screening.

Concomitant medications:

18. Fibrates are not permitted from 2 months before Randomization. Patients that used statins, ezetimibe, or other nonfibrate lipid lowering drugs before Screening may participate if the dosage has been kept constant for at least 2 months prior to Screening.
19. Currently taking drugs that can induce steatosis/steatohepatitis including, but not restricted to: corticosteroids (parenteral & oral chronic administration only), amiodarone (Cordarone), tamoxifen (Nolvadex), and methotrexate (Rheumatrex, Trexall), which are not permitted 30 days prior to Screening and up to end of treatment.
20. Currently taking any medication that could interfere with study medication absorption, distribution, metabolism, or excretion or could lead to induction or inhibition of microsomal enzymes, e.g., indomethacin, which are not permitted from Randomization until end of treatment.

Associated illnesses or conditions:

21. Any medical conditions that may diminish life expectancy to less than 2 years including known cancers.
22. Evidence of any other unstable or, untreated clinically significant immunological, endocrine, hematological, gastrointestinal, neurological, neoplastic, or psychiatric disease
23. Mental instability or incompetence, such that the validity of informed consent or ability to be compliant with the study is uncertain.

In addition to the above criteria, patient should not present any of the following biological exclusion criteria:

24. Positive anti-human immunodeficiency virus antibody.
25. Aspartate aminotransferase (AST) and/or ALT >10 x upper limit of normal (ULN).
26. Conjugated bilirubin > 1.50mg/dL due to altered hepatic function **Note**: Gilbert Disease patients are allowed into the study.
27. International normalized ratio >1.40 due to altered hepatic function.
28. Platelet count <100,000/mm^3 due to portal hypertension.

29. Serum creatinine levels >1.53 mg/dL in males and >1.24 mg/dL in females.
30. Significant renal disease, including nephritic syndrome, chronic kidney disease (defined as patients with markers of kidney damage or estimated glomerular filtration rate [eGFR] of less than 60 ml/min/1.73 m^2).
31. Unexplained serum creatine phosphokinase (CPK) >3 x the ULN. In case of explained elevated CPK >3 x the ULN, the measurement can be repeated prior to Randomization. In this case, retest should be performed within 1 to 2 weeks after initial test. A CPK retest >3 x ULN leads to exclusion.

Criteria for Evaluation:

Primary endpoint

Surrogate endpoint - resolution of NASH (at surrogate endpoint analysis)

To evaluate the efficacy of elafibranor 120 mg versus placebo on the resolution of NASH without worsening of fibrosis after 72 weeks of treatment.

Long-term endpoint – clinical outcomes (at final analysis)

To evaluate the efficacy of elafibranor 120 mg QD versus placebo on clinical outcomes described as a composite endpoint composed of death due to any cause, histological liver cirrhosis, and the full list of portal hypertension/cirrhosis related events:

- liver transplantation
- MELD score ≥15
- HCC
- the onset of:
    - variceal bleed
    - hepatic encephalopathy
    - spontaneous bacterial peritonitis
    - ascites
    - hepatorenal syndrome
    - hepatopulmonary syndrome
    - chronic gastrointestinal blood loss due to portal hypertensive gastropathy (provided that these lead to hospitalization or transfusion).

The final analysis will be performed when 456 patients experience an event listed above. This is expected to occur approximately 96 months after the first patient is randomized.

Key secondary endpoints (at surrogate endpoint analysis)

Percentage of patients with improvement of fibrosis of at least 1 stage according to NASH CRN scoring at 72 weeks.

Changes from baseline to Week 72 in triglycerides, Non-HDL cholesterol, HDL cholesterol, LDL cholesterol, HbA1c (in diabetic patients), HOMA-IR (in non-diabetic patients)

Other secondary endpoints

- To assess histological changes after 72 weeks of treatment and at the end of the LTTP on the following endpoints:
    - percentage of patients with resolution of NASH without worsening of fibrosis (at the end of LTTP)
    - percentage of patients with improvement of fibrosis of at least 1 stage according to NASH CRN scoring (at the end of LTTP)
    - percentage of patients with improvement of fibrosis of at least 1 stage according to NASH CRN scoring without worsening of NASH
    - percentage of patients with no worsening of fibrosis and no worsening of NASH
    - percentage of patients with resolution of NASH and improvement of Fibrosis
    - percentage of patients with at least a 1 point improvement in histological scores (NASH CRN scoring: NAS [sum of steatosis, hepatic ballooning and lobular inflammation], steatosis, hepatic ballooning, lobular inflammation), fibrosis (NAFLD Ishak scoring system), or portal inflammation
    - percentage of patients with improvement of NAS of at least 2 points
    - percentage of patients with improvement of NAS of at least 2 points and with at least 1 point improvement in hepatic ballooning
    - percentage of patients with at least a 1 point improvement in disease activity score (sum of ballooning and lobular inflammation scores) according to NAS scoring and steatosis-activity-fibrosis (SAF) scoring

  - percentage of patients with at least a 1 point improvement in disease activity score (sum of ballooning and lobular inflammation scores) according to NAS scoring and with at least 1 point improvement in hepatic ballooning
  - percentage of patients with at least a 1 point improvement in disease activity score (sum of ballooning and lobular inflammation scores) according to steatosis-activity-fibrosis (SAF) scoring and with at least 1 point improvement in hepatic ballooning
  - percentage of patients with at least 2 points improvement in disease activity score according to NAS scoring and SAF scoring
  - changes in NAS, fibrosis (using NASH CRN and NAFLD Ishak scoring system), steatosis, hepatic ballooning, lobular inflammation, portal inflammation, SAF activity score
  - changes in area of fibrosis (normalized Collagen Proportional area in %) by morphometry.
- To assess the following endpoints at Week 72, and at the end of the LTTP:
  - changes in liver enzymes and liver markers
  - changes in noninvasive markers of fibrosis and steatosis
  - changes in lipid parameters
  - variation in body weight
  - changes in insulin resistance and glucose homeostasis markers
  - changes in inflammatory markers
  - changes in cardiovascular risk profile as assessed by Framingham scores
  - changes in liver stiffness by Fibroscan measurement
  - changes in quality of life (SF-36 questionnaire).
- To assess the onset of:
  - histological liver cirrhosis
  - death of any cause
  - any portal hypertension or cirrhosis related events
  - cardiovascular events
  - liver-related death events.

Exploratory endpoints

- To constitute a biobank for discovery and validation of biomarkers in NASH.

Study Duration (planned): estimated 72 months (First Patient First Visit [FPFV]-Last patient last visit [LPLV])

- Regulatory/ethics committee submission: January 2016
- Initiation visits: March 2016 – Sep 2018
- Recruitment period: March 2016 – May 2020
- FPFV: March 2016
- Surrogate endpoint analysis: Q1 2020 – Q2 2020
- LPLV (LTTP): estimated within Q1 2024

Data Safety Monitoring Board (DSMB)

An independent DSMB will be established in order to review the progress of the study and to perform a safety data review on a regular basis during the trial to protect patient welfare and preserve study integrity. The DSMB will also review the interim analysis results and provide final recommendations regarding trial termination due to futility and adjustment of the target number of primary events.

The DSMB will consist of at least 5 experienced physicians (1 endocrinologist, cardiologist, hepatologist, oncologist, and nephrologist) and 1 statistician, all of whom will be independent of the participants in the study. The DSMB Charter will define the role, responsibilities, rules, and tasks of the DSMB.

Clinical events committee (CEC)

The CEC will conduct the adjudication of all disease progression events included in the primary composite efficacy long-term endpoint (except for histological cirrhosis), all drug-induced liver injury events, and all major cardiovascular events as defined in the CEC charter. The CEC assessment and adjudication will occur in a blinded, consistent, and unbiased manner throughout the course of a study to determine whether the endpoints meet the protocol-specified criteria.

The CEC will be comprised of 2 hepatologists, 2 cardiologists, and 1 endocrinologist all of whom will be independent of the participants in the study.

Table 1: STUDY GENERAL ASSESSMENT SCHEDULE

	Screening Period			First Treatment Period							Long-term Treatment Period		End Of Study Treatment
Visit	**SV1[4]**	**SV2[4]**	**SPV[5]**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**Phone Visit PV1-PVn**	**V8-Vn**	**EOT[13]**
Week	*-12 to -1*		*-1*[5]	*0*[6]	*12*[6]	*24*[6]	*36*[6]	*48*[6]	*60*[6]	*72*[6]	*(every 24 weeks starting 12 weeks after V7)*[8]	*(every 24 weeks starting after V7)*[9]	*30 days after final study drug administration*
Permitted Margin				0	± 1 week after V1	± 1 week after V1	± 1 week after V1	± 1 week after V1	± 1 week after V1	± 1 week after V1	± 2 weeks Compared to V7	± 2 weeks Compared to V7	± 1 week after last administration
Obtain informed consent	X												
Medical history / demographics	X												
Check inclusion / exclusion criteria	X			X[7]									
Adequate diet and lifestyle recommendations, including alcohol restrictions and smoking habits	X - - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - →	
Confirmation of diet and lifestyle compliance, including alcohol restrictions and smoking habits				X	X	X	X	X	X	X	X	X	X
Physical examination	X			X	X	X	X	X	X	X		X	X
Vital signs & height[1] & weight measurement	X			X	X	X	X	X	X	X		X	X
Waist circumference	X			X		X		X		X		X	X

	Screening Period			First Treatment Period							Long-term Treatment Period		End Of Study Treatment
Visit	**SV1[4]**	**SV2[4]**	**SPV[5]**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**Phone Visit PV1-PVn**	**V8-Vn**	**EOT[13]**
Week	*-12 to -1*		*-1[5]*	*0[6]*	*12[6]*	*24[6]*	*36[6]*	*48[6]*	*60[6]*	*72[6]*	*(every 24 weeks starting 12 weeks after V7)[8]*	*(every 24 weeks starting after V7)[9]*	*30 days after final study drug administration*
Permitted Margin				**0**	**±1 week after V1**	**± 1 week after V1**	**± 1 week after V1**	**± 1 week after V1**	**± 1 week after V1**	**± 1 week after V1**	**± 2 weeks** Compared to V7	**± 2 weeks** Compared to V7	**± 1 week** after last administration
12-Lead ECG				X			X			X		X[10]	X
Lab evaluation (see Table 2)	X	X		X	X	X	X	X	X	X		X	X
Send sample for central histological evaluation of NASH diagnosis / change	X	X								X		X[11]	
Liver biopsy		X[4]								X		X[11]	
Phone call to patient to confirm eligibility of histology criteria			X[5]										
FibroScan[2]				X						X		X	
Contact the patient prior to visit[3]				X	X	X	X	X	X	X		X	X
Randomization				X									
IXRS registration	X			X	X	X	X	X	X	X	X	X	X
Review prior / concomitant medication	X			X	X	X	X	X	X	X	X	X	X
Quality of life assessment				X		X		X		X		X[12]	X

	Screening Period			First Treatment Period							Long-term Treatment Period		End Of Study Treatment
Visit	**SV1**[4]	**SV2**[4]	**SPV**[5]	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**Phone Visit PV1-PVn**	**V8-Vn**	**EOT**[13]
Week	*-12 to -1*		*-1*[5]	*0*[6]	*12*[6]	*24*[6]	*36*[6]	*48*[6]	*60*[6]	*72*[6]	*(every 24 weeks starting 12 weeks after V7)*[8]	*(every 24 weeks starting after V7)*[9]	*30 days after final study drug administration*
Permitted Margin				**0**	**±1 week after V1**	**± 1 week after V1**	**± 1 week after V1**	**± 1 week after V1**	**± 1 week after V1**	**± 1 week after V1**	**± 2 weeks** Compared to V7	**± 2 weeks** Compared to V7	**± 1 week** after last administration
Adverse events	X	X		X	X	X	X	X	X	X	X	X	X
Data collection on clinical outcomes					X	X	X	X	X	X	X	X	X
Study placebo or drug dispensation				X	X	X	X	X	X	X		X	
Drug accountability					X	X	X	X	X	X	X	X	X

Abbreviations: ECG = electrocardiogram; EOT = end of treatment; IXRS = Interactive voice/web Response System; LTTP = Long-term Treatment Period; NASH = nonalcoholic steatohepatitis; PV = phone visit; QOL = quality of life; SV = Screening visit; V = visit

1. Height is measured only at visit SV1.
2. Where possible FibroScan must be done at the day of visit. Otherwise, it can be performed within 7 days around the visit date.
3. During the study, the patient should be contacted at least 1 week before the next visit as a reminder on procedures and IP return.
4. The visits to be performed during the screening period should be scheduled according to the following requirements:
   - If there are historical lab values for AST, ALT, total bilirubin and INR that are within 8 weeks to 6 months of the planned Randomization visit (V1) these results can be used as the first baseline values in case of DILI adjudication. If there are no historical lab values that meet this requirement, then SV1 and V1 must be scheduled at least 8 weeks apart.
   - The visit SV2 only occurs if no historical biopsy within 6 months before the Screening Visit is available. A screening liver biopsy and slides shipment to the central pathologist must be performed at least 4 weeks before Randomization, in order to obtain the results in time. However, in some exceptional cases, the central reading process can be expedited allowing a shorter time between SV1 or SV2 and V1. Coagulation (platelet count and PT [INR]) should be checked locally prior to this liver biopsy (according to local medical standards in each hospital).

- Randomization visit can be scheduled as soon as all the results are available to confirm the eligibility of the patients

5. Screening Phone Visit. Telephone contact for all patients at least 1 week before V1. Patients should be contacted regarding eligibility confirmation within 1 week prior to Randomization Visit V1. In case of ineligibility, the patient should be contacted as soon as possible.

6. The maximum time period between visits in the First Treatment Period is to be 96 days due to the study drug supply provided to the patient.

7. Check of all inclusion/exclusion criteria, including biological and histological criteria assessed at SV1 and SV2.

8. Phone visits every 24 weeks starting 12 weeks after V7 for safety, data collection on clinical outcomes, and IP compliance control. If any information during this phone contact requires a visit, the Investigator may decide to perform an unscheduled visit. Phone visits may also be performed at the same frequency for the follow-up of patients having permanently discontinued study drug but remaining in the study (Same information collected except IP compliance control).

9. The maximum time period between visits in the Long-term Treatment Period (LTTP) is to be 192 days due to the study drug supply provided to the patient.

10. In the LTTP the first ECG will be performed at V9 and then every 48.

11. Liver biopsy will be performed after approximately 4 years of treatment (V13) and in the case of suspicion of cirrhosis (based on FibroScan and/or clinical or biological assessment). In the case that the suspicion of cirrhosis is not confirmed by liver biopsy the patient shall remain on the study and a liver biopsy will be performed after approximately 4 years of treatment (V13, unless a biopsy has already been performed within the year). Blood sampling (coagulation tests; see Table 2) are to be performed locally before the biopsy.

12. QOL assessment questionnaire to be completed at 24 (V8), 48 (V9), and 96 (V11) weeks in the LTTP (following approximately 96, 120, and 168 weeks of treatment, respectively), and every 48 weeks thereafter.

13. EOT Visit to be performed 30 days after final study drug administration at the end of study or for any premature discontinuation (permanent study drug discontinuation or trial discontinuation).

Table 2: STUDY BIOLOGICAL ASSESSMENT SCHEDULE

Visit	Screening Period		First Treatment Period							Long-term Treatment Period	End of Study Treatment
	SV1 SB1[6]	SB2[7]	V1 B1	V2 B2	V3 B3	V4 B4	V5 B5	V6 B6	V7 B7	V8 to Vn B8 to Bn	EOT
Week	*-12 to -1*	*Prior to liver biopsy*	*0*	*12*	*24*	*36*	*48*	*60*	*72*	*Every 24 weeks*	*30 days after final study drug administration*
Hematology *Hemoglobin, hematocrit, RBC, WBC, differential count, platelet count, reticulocytes count, and PT (INR)*	X		X	X	X	X	X	X	X	X	X
Coagulation - local lab testing prior to liver biopsy *Platelet count, PT (INR)*[1]		X							X	X[1]	
Serology *HIV ab I/II, HBsAg, and HCV Ab (positive HCV RNA in case HCV Ab >0 or known cured hepatitis C infection*[2]*)*	X										
Screening Visit 1 - chemistry panel *HbA1c*[2]*, fasting plasma glucose, insulin (fasting), HOMA-IR creatinine, eGFR, GGT, AST, ALT, CPK*[2]*, alkaline phosphatase, total and conjugated bilirubin, sodium, TG, and MELD score*	X										
V1 to Vn total chemistry panel *HbA1c, fasting plasma glucose, creatinine, eGFR, GGT, AST, ALT, CPK, alkaline phosphatase, total proteins, albumin, electrolytes (sodium, potassium, chloride, calcium), uric acid, urea (BUN), total and conjugated bilirubin, hsCRP, total cholesterol, nonHDL-C, HDL-C, TG, calculated VLDL-C, ApoAI, ApoB, calculated LDL-C, and MELD score*			X[6]	X	X	X	X	X	X	X	X

Visit	Screening Period		First Treatment Period							Long-term Treatment Period	End of Study Treatment
	SV1 SB1[6]	SB2[7]	V1 B1	V2 B2	V3 B3	V4 B4	V5 B5	V6 B6	V7 B7	V8 to Vn B8 to Bn	EOT
Week	*-12 to -1*	*Prior to liver biopsy*	*0*	*12*	*24*	*36*	*48*	*60*	*72*	*Every 24 weeks*	*30 days after final study drug administration*
Urinalysis *albumin, creatinine, ACR, and microscopic analysis α1 microglobulin*, β-NAG,* N-Gal*, IL-18*, KIM-1*,*			X	X	X	X	X	X	X	X	X
Urinalysis (dipstick) *Specific gravity, pH, protein, glucose, ketones, bilirubin, urobilinogen, blood, nitrite, and leukocytes*	X		X	X	X	X	X	X	X	X	X
Urinary pregnancy tests [3]	X		X	X	X	X	X	X	X	X	X
Inflammatory markers *Fibrinogen, and haptoglobin*			X		X		X		X	X	X
Other Liver markers *CK18 (M65 & M30), adiponectin, ferritin, FGF19 & FGF21, alpha2 macroglobulin, hyaluronic acid, PIIINP, TIMP-1, and CHI3L1* [4]			* [4]		*		*		* [4]	* [4]	*
Calculated fibrosis & steatosis index *Fibrotest, ELF, NAFLD Fibrosis score, Steatotest, FLI, Fibrometre S, and FIB-4*			*		*		*		*	*	*
Other safety markers *Homocysteine, NT-ProBNP, troponin-T, and cystatin C*			*		*		*		*	*	*
Special glycemic and other lipid parameters *Insulin(fasting), HOMA-IR, Fructosamine, C-peptide, FFA, small dense LDL, ApoAII, Apo CIII, and Apo E*			*		*		*		*	*	*

Visit	Screening Period		First Treatment Period							Long-term Treatment Period	End of Study Treatment
	SV1 SB1[6]	SB2[7]	V1 B1	V2 B2	V3 B3	V4 B4	V5 B5	V6 B6	V7 B7	V8 to Vn B8 to Bn	EOT
Week	*-12 to -1*	*Prior to liver biopsy*	*0*	*12*	*24*	*36*	*48*	*60*	*72*	*Every 24 weeks*	*30 days after final study drug administration*
Sampling for additional parameters *Whole blood[5], plasma, and serum bank*	* [5]		*	*	*	*	*	*	*	*	*

X = results available within 2 working days (routine analysis) * = batch analysis

Abbreviations Ab = antibody; ACR = albumin–creatinine ratio; Ag = antigen; ALT = alanine aminotransferase; Apo = apolipoprotein; AST = aspartate aminotransferase; β-NAG = N-acetyl-β-D-glucosaminidase; BUN = blood urea nitrogen; B = biological assessment Visit; CHI3L1 = chitinase-3-like protein 1; CK18 = cytokeratin 18; CPK = creatine phosphokinase; eGFR = estimated glomerular filtration rate; ELF = enhanced liver fibrosis; EOT = end of study treatment; FFA = free fatty acid; FGF = fibroblast growth factor; FIB-4 = fibrosis 4 score; FLI = fatty liver index; GGT = gamma-glutamyl transferase; HbA1c = hemoglobin A1c; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HDL-C = high density lipoprotein-C; HIV = human immunodeficiency virus; HOMA-IR = homeostasis model assessment of insulin resistance; hsCRP = high-sensitivity C-reactive protein; IL-18 = interleukin 18; INR = international normalized ratio; KIM-1 = kidney injury molecule-1; LDL-c = low density lipoprotein-C; MDRD = modification of diet in renal disease; MELD = model end stage liver disease; NAFLD = nonalcoholic fatty liver disease; N-Gal = neutrophil gelatinase-associated lipocalin; NT-ProBNP = N-terminal of the prohormone brain natriuretic peptide; PIIINP = type III procollagen peptide; PT = prothrombin time; TIMP-1 = tissue inhibitors of metalloproteinases 1; RBC = red blood cell; SB = Screening biological assessment Visit; SV = Screening Visit; TG = triglyceride; VLDL-C = very low density lipoprotein-C; V = Visit; WBC = white blood cell.

1. Coagulation (platelet count and PT [INR]) should be checked prior to any liver biopsy (according to local medical standards in each hospital). To be done through a local laboratory. Liver biopsy will be performed after 72 weeks (V7) and after approximately 4 years of treatment (V13) and in the case of suspicion of cirrhosis (based on FibroScan and/or clinical or biological assessment). In the case that the suspicion of cirrhosis is not confirmed by liver biopsy the patient shall remain on the study and a liver biopsy will be performed after approximately 4 years of treatment ([V13] unless a biopsy has already been performed within the past year).
2. Upon receipt of the results of the biological assessment performed at SV1, retesting or additional testing may be needed during the Screening Period:

- CPK can be repeated prior to Randomization (V1) within 1 to 2 weeks after initial test.
- HbA1c can be repeated prior to Randomization (V1), at the latest 2 weeks prior to planned Randomization.
- HCV RNA can be tested, at SV1 in case of known cured hepatitis c infection, or in case of positive HCV Ab at SV1, at a retest screening visit at the latest 2 weeks prior to the planned Randomization (V1).

3. Dipstick at site for WOCBP only. In addition, home pregnancy tests are to be performed by WOCBP every 4 weeks from V1 (see Table 1 and Figure 2).
4. CHI3L1 to be tested only at V1, V7, and at the time of 4 years biopsy (V13).

5. Whole blood sample will be only taken at SV1 while plasma and serum samples are to be taken at every visit **ONLY** for patients who have signed the pharmacogenomic and biomarker ICF.

6. If no historical values of AST, ALT, total bilirubin and INR meeting the requirements of within 8 weeks to 6 months of planned randomization visit (V1) are available, then SV1 and V1 must be scheduled at least 8 weeks apart in order to have 2 consecutive values for DILI adjudication. In any case, the visits should be scheduled in order to obtain the needed results prior to the randomization.

7. SB2, additional visit in the Screening Period if required for coagulation prior to liver biopsy.

Figure 1: STUDY DURATION AND VISIT SCHEDULE

Figure 2: PREGNANCY TESTING SCHEDULE FOR WOMEN OF CHILDBEARING POTENTIAL

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LIST OF ABBREVIATIONS

AASLD	American Association for the Study of Liver Diseases
ACR	albumin–creatinine ratio
ADR	adverse drug reaction
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	Analysis of Covariance
ApoAI	apolipoprotein AI
ApoAII	apolipoprotein AII
ApoB	apolipoprotein B
ApoCIII	apolipoprotein CIII
AST	aspartate aminotransferase
AT	aminotransferase
ATP	Adult Treatment Panel
BMI	body mass index
BP	blood pressure
BUN	blood urea nitrogen
Bx	biological assessment visit
CA	competent authorities
CEC	Clinical Events Committee
CFR	Code of Federal Regulations
CPK	creatine phosphokinase
CRN	Clinical Research Network
CRO	Clinical Research Organization
CRP	C-reactive protein
CSR	Clinical Study Report
CYP	cytochrome P450
DDI	drug-drug interaction
DILI	drug-induced liver injury
DSMB	Data Safety Monitoring Board
DSUR	Development Safety Update Report
EASL	European Association for the Study of the Liver
ECG	electrocardiogram
eCRF	electronic case report form
EES	efficacy evaluable sample
eGFR	estimated glomerular filtration rate
EOS	end of study
EOT	end of study treatment
FDA	Food and Drug Administration
FFA	free fatty acid
FIB-4	fibrosis 4 score
FITT	full intent-to-treat set
FLI	fatty liver index
FPFV	first patient first visit
FSS	full safety set
GCP	Good Clinical Practice

GGT	gamma-glutamyl transferase
GLP1	glucagon-like peptide 1
HbA1c	hemoglobin A1c
HBsAg	hepatitis B surface antigen
HCC	hepatocellular carcinoma
HCV	hepatitis C Virus
HDL-C	High-density lipoprotein cholesterol
HIV	human immunodeficiency virus
HOMA-IR	homeostasis model assessment of insulin resistance
hPPAR	human peroxisome proliferator-activated receptor
HRT	Hormonal replacement therapy
HSC	hepatic stellate cells
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
INR	international normalized ratio
IP	investigational product
IQR	InterQuartile Range
IR	insulin resistance
IRB	Institutional Review Board
ITT	intent-to-treat
IXRS	Interactive Voice/Web Response System
LDL-C	Low-density lipoprotein cholesterol
LPLV	last patient last visit
[redacted]	[redacted]
LTTP	Long-term Treatment Period
M2	anti-inflammatory macrophages
MedDRA	Medical Dictionary for Regulatory Activities
MELD	model end stage liver disease
NAFL	nonalcoholic fatty liver
NAFLD	nonalcoholic fatty liver disease
NAS	NAFLD Activity Score
NASH	nonalcoholic steatohepatitis
NCEP ATP III	National Cholesterol Education Program's Adult Treatment Panel III
PBC	Primary Biliary Cholangitis
PD	pharmacodynamic
PK	pharmacokinetic
PPAR	peroxisome proliferator-activated receptor
PPS	per protocol set
PT	prothrombin time
PUFA	polyunsaturated fatty acids
QD	once daily
QTc	corrected QT
SADR	serious adverse drug reaction
SAE	serious adverse event
SAF	steatosis-activity- fibrosis
SAP	Statistical Analysis Plan

SBx	screening biological assessment visit
SF-36	36-Item Short-Form Health Survey
SGLT2	sodium/glucose cotransporter 2
SOP	Standard Operating Procedure
SS	safety set
SUSAR	suspected unexpected serious adverse reactions
SVx	Screening Visit x
TLC	therapeutic lifestyle change
TNFα	Tumor Necrosis Factor-alpha
UDCA	UrsoDeoxyCholic Acid
ULN	upper limit of normal
UV-LLNA	UV- Local Lymph Node Assay
Vx	Visit x
WOCBP	women of childbearing potential

1. INTRODUCTION

1.1. NONALCOHOLIC STEATOHEPATITIS

Nonalcoholic fatty liver disease (NAFLD) is a spectrum of disorders characterized by excessive fat accumulation in the liver (steatosis). Nonalcoholic steatohepatitis (NASH) defines a subgroup of NAFLD where steatosis coexists with hepatocyte injury and inflammation (steatohepatitis), with or without fibrosis.

Nonalcoholic steatohepatitis is considered by the European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Diseases (AASLD) as an increasing public health issue owing to its close epidemiological association with the worldwide epidemic of obesity and type 2 diabetes.

The prevalence of NAFLD in the general population assessed by ultrasonography is 20% to 30% in Europe. A similar prevalence of 15% to 25% was documented histologically by postmortem studies. A high prevalence of histological NAFLD has been described in apparently healthy liver donors: 12% to 18% in Europe and 27% to 38% in the US. Furthermore, with a sensitive technique such as magnetic resonance spectroscopy, 34% have NAFLD.

Interestingly, 39% of newly diagnosed cases of chronic liver disease had NAFLD, making NASH one of the top causes of liver diseases in Western countries. Using the histological definition of NASH, recent studies have shown a high prevalence of NASH among NAFLD cases: 43% to 55% in patients with increased aminotransferases (ATs), 49% in morbidly obese patients, and 67% in a subset of patients with incident chronic liver disease. Finally, in apparently healthy liver donors the prevalence of NASH ranges from 3% to 16% in Europe and from 6% to 15% in the US.

The commonest cause of NASH is primary NAFLD-associated insulin resistance and its phenotypic manifestations, namely excess weight/obesity, visceral obesity, type 2 diabetes, hypertriglyceridemia, and arterial hypertension. A causal association has been suggested by longitudinal studies showing a chronological association between the progression of insulin resistance, the metabolic syndrome, and the occurrence of NAFLD/NASH.

1.2. PATHOPHYSIOLOGICAL PROCESS OF NONALCOHOLIC STEATOHEPATITIS

A widely described model suggests that the development of NAFLD into NASH requires several 'hits' or insults.[1,2] According to this model, increased hepatic levels of free fatty acid (FFA) consequent to impaired insulin sensitivity in the liver and peripheral tissues may serve as the first hit. The increased hepatocyte FFA load would further increase insulin resistance (IR), steatosis, oxidative stress with lipid peroxidation, endoplasmic reticulum stress, resulting in inflammatory cell accumulation and activation into the liver (second hit). This finally leads to hepatocyte growth arrest or apoptosis, which activates hepatic progenitor cells and associated bile ductular proliferations, cells that initiate inadequate repair by producing a diverse range and high concentrations of profibrogenic cytokines and growth factors that activate hepatic stellate cells (HSC)

and perivascular or portal fibroblasts. The activated HSC themselves can release chemotactic factors that recruit inflammatory cells, creating a deleterious feedback inflammatory loop that leads to fibrogenesis. Collagen and other extracellular matrix components accumulate within the liver, which may result in distortion of the hepatic architecture and finally cirrhosis. Thus, in this "multiple-hit" model IR can be considered as the first step on the pathogenic road leading to NASH, fibrosis and cirrhosis.

However, this "multiple-hit" model has been recently challenged by data suggesting that mechanisms that can drive disease progression can also induce steatosis. Oxidative stress and gut flora/cytokines can induce steatosis as well as necroinflammation and fibrosis. Free fatty acids can initiate hepatocyte apoptosis in addition to being esterified to triglycerides. Endoplasmic stress can also lead to steatosis, oxidative stress, and apoptosis. Since all these mechanisms are important in obesity and IR, it would seem likely that they are the true "first hits" leading to increased hepatic FFA flux and oxidative-, endoplasmic reticulum-, and cytokine-mediated stress that result in both steatosis and progressive liver damage. Steatosis should therefore be considered part of the liver's early "adaptive" response to stress, rather than a first hit in disease progression. Accordingly, while in some situations its severity may act as a biomarker of ongoing injurious and fibrotic mechanisms resulting in disease progression, it should not be considered a sole therapeutic target. Instead attention should be paid on the mechanisms of cellular injury and fibrosis – the "second hits."

Oxidized by-products are harmful adducts that can cause liver injury, resulting in subsequent fibrosis.[3] Lipid peroxidation and oxidative stress up-regulate liver fibrosis via activation of stellate cells and increased production of Transforming Growth Factor-beta.[4] Over expression of uncoupling proteins has been associated with a reduction in generation of reactive oxygen species and Kupffer cell activation, which might attenuate injury in NAFLD. In addition to insulin resistance, several authors have shown that leptin contributes to an insulin-resistant state and might even stimulate fibrogenesis in animal models of NAFLD.[5]

Inflammatory mediators have been implicated in the progression of NAFLD and are the focus for new therapeutics. Pro-inflammatory transcription factors such as Nuclear Factor kappa B (NF-κB) are often elevated in patients with NASH.[6] Adiponectin decreases fatty acid oxidation and inhibits hepatic gluconeogenesis.7 Both human and mouse models have demonstrated that lower adiponectin levels are associated with increased severity of hepatic inflammation.[8,9] Tumor Necrosis Factor (TNF)α is an inflammatory mediator largely produced by macrophages, but also elaborated by other cells including adipocytes and hepatocytes.[1,10] Elevated levels of TNFα have been detected in obese patients with insulin resistance and NASH.[11,12] TNFα-mediated hepatic injury results from inhibition of mitochondrial electron transport and release of reactive oxygen species that stimulate lipid peroxidation.[10]

Recently, scientists have focused on the role of Kupffer cells in the pathogenesis of NAFLD. Kupffer cells are the resident macrophages of the liver and function in both innate and adaptive immunity as active phagocytosing agents and antigen-presenting cells (via toll-like receptors) to T-cells. Finally, the proapoptotic gene Bax is upregulated in patients with NASH and alcoholic liver disease.[13] Additionally, caspase levels, by-products of cellular apoptosis, are also increased in these groups of patients.

1.3. ELAFIBRANOR: RATIONALE FOR A MIXED PPAR ALPHA/DELTA AGONIST IN NASH

The GENFIT drug candidate, elafibranor, and its main active circulating metabolite, GFT1007, are dual peroxisome proliferator-activated receptor (PPAR)α/δ modulators with preferential activity on PPARα over PPARδ (about fivefold more potent on human PPAR [hPPAR]α than on hPPARδ). The PPARδ properties of elafibranor and GFT1007 have been demonstrated in both human skeletal muscle cells (a pure PPARδ response) and human hepatocytes (a mixed PPARα/δ response).

The PPARα receptors are most prominently expressed in the liver and can be activated by drugs of the fibrate class. Activation results in increased uptake and oxidation of FFAs, increased triglyceride hydrolysis and upregluation of apolipoprotein (Apo)A-I and ApoA-II. The net effect is fatty acid oxidation, decrease in serum triglycerides, a rise in high-density lipoprotein cholesterol (HDL-C) levels, and an increase in cholesterol efflux. The PPARα activation has also anti-inflammatory effects via inhibition of COX2, IL-6, and C-reactive protein (CRP). Some PPARα compounds have proved their effectiveness in animal models like Methionine-Choline-Deficient diet model or CCl4 in reducing the steatosis. However, clinical trials with fibrates in human NASH have been unimpressive. For example in a pilot study, 12 months treatment with clofibrate in 16 patients with NASH and elevated triglycerides had no impact on liver enzyme elevation or triglycerides levels.[14]

The PPARδ appears to be a powerful metabolic regulator, with actions on fat, skeletal muscle, liver, and heart. Its activation enhances fatty acid transport and oxidation, improves glucose homeostasis via improved insulin sensitivity and inhibition of hepatic glucose output, turns off macrophage inflammatory responses, and dramatically increases circulating HDL-C levels. Thus selective PPARδ agonists have the potential to target multiple components of the metabolic syndrome, including obesity, dyslipidemia, hypertriglyceridemia insulin resistance, and probably NASH.

Accordingly, PPARδ ligands also show promise in chronic inflammatory models of hepatotoxicity.[15] Notably, biomarkers of liver toxicity, including serum alanine aminotransferase (ALT), hepatic TNFα, TNF-like weak inducer of apoptosis receptor, were all higher in carbon tetrachloride-treated PPARδ knockout mice compared to wild-type mice. GW0742 reduced serum ALT, TNFα, S100A6, MCP1, and TNF-like weak inducer of apoptosis receptor in wild-type mice, but not PPARδ knockouts.

Finally, in a short clinical trial, a pure PPARδ agonist, GW501516, has demonstrated efficacy on liver fat content while improving insulin resistance and decreasing γGT.[16]

Considering the emerging role of Kupffer cells in the pathogenesis, 2 recent publications identified PPARδ as a crucial signaling receptor controlling the phenotypic switch between classical pro-inflammatory and alternative anti-inflammatory (M2) macrophages.[17,18] These studies demonstrate that PPARδ encourages macrophages toward the alternative M2 phenotype, which improves fatty acid metabolism, insulin sensitivity, and suppresses inflammation. The finding raise the possibility that small molecule agonist of PPARδ may be effective therapeutic targets for the treatment of chronic inflammation in the liver.

The match between the activation of PPARα and PPARδ in the liver may thus improve NASH. Accordingly, in several well-established experimental models of NAFLD/NASH and liver fibrosis, treatment with elafibranor confers liver protection both in preventive and therapeutic approaches on established pathologies. These effects have been demonstrated through plasma and hepatic markers, as well as liver macro- and micro-histological examination. These studies have shown that elafibranor acts on several mechanisms involved in NASH pathogenesis: steatosis, inflammation, and fibrosis pathways. Complementary studies have demonstrated that both PPARα-dependent and PPARα-independent mechanisms participate in the beneficial effects of elafibranor on NAFLD/NASH.

1.4. SUMMARY OF NONCLINICAL STUDIES

1.4.1. Pharmacology

Besides hepatoprotection, the efficacy of elafibranor has been assessed in numerous pharmacological preclinical models of metabolic disorders. Briefly, in experimental models of type 2 diabetes, elafibranor has insulin-sensitizing and glucose lowering properties. In db/db mice, a 28-day treatment with elafibranor produced a dose-dependent decrease in fasting plasma glucose and glycated hemoglobin (HbA1c), comparable to the effect of rosiglitazone. However, in contrast to the PPARγ reference agonist, elafibranor did not increase plasma adiponectin, thus ruling out a PPARγ -mediated effect on adipose tissues. Similarly, in ob/ob mice, elafibranor ameliorated plasma glucose and insulin levels without modulating plasma adiponectin or inducing PPAR target genes in adipose tissues.

Besides its effects on NAFLD/NASH and type 2 diabetes, oral treatment with elafibranor in a mouse model of dyslipidemia potently reduced plasma triglycerides and total cholesterol through the induction of PPARα target genes in the liver and by reduction of ApoCIII gene expression. In parallel, elafibranor increased plasma HDL-C levels more potently than the PPARα reference compound fenofibrate. The chronic treatment of these mice fed a high fat diet with elafibranor prevented the development of atherosclerotic plaques in the aorta.

1.4.2. Safety pharmacology

Any potential effect on the cardiovascular, respiratory, and central nervous system has been assessed and no safety issue was identified.

1.4.3. Absorption/distribution/metabolism/excretion studies (ADME)

In animal studies, elafibranor was well and rapidly absorbed although absolute bioavailability was moderate (about 20% to 40%). Elafibranor is extensively metabolized and the activity is mainly carried by the active metabolite GFT1007. In rat and dog, maximal plasma concentrations and exposure for both elafibranor and GFT1007 linearly increase with the dose after single or repeated administrations. Elafibranor and its metabolites are rapidly cleared from the plasma and they are totally excreted by both fecal and renal route within 48 hours. In the rat elafibranor and/or its metabolites are rapidly excreted into the bile and undergo

an extensive entero-hepatic cycle giving support for liver targeting of elafibranor and/or GFT1007. The distribution study in the rat supports the liver targeting of elafibranor and/or its metabolites.

In vitro elafibranor does not inhibit cytochrome p450 (CYP)1A2, CYP3A4, and CYP2D6 with moderate inhibition of CYP2C9 and weak inhibition of CYP2C8, CYP2C19, and CYP4A11. GFT1007 does not produce any inhibition of the CYP450 isoforms 1A2, 3A4, 2C19, and 2D6, and only weak inhibition of CYP2C8 and CYP2C9. Both molecules also show weak inhibition of CYP3A4/5, but only with midazolam as substrate. Thus, the risk of drug-drug interaction due to an inhibition of the main cytochromes involved in drug metabolism should be limited. Potential interaction with CYP2C9 metabolized drugs has been assessed through a clinical study (GFT505-112-8) designed to evaluate potential pharmacokinetic (PK) interaction of elafibranor 120 mg administered for 14 days alone or with a single administration of warfarin. This study demonstrated that elafibranor administration did not affect the PK profile of warfarin (R-warfarin and S-warfarin).

A protein binding study showed that elafibranor and GFT1007 were highly bound to human serum albumin. The risk of drug-drug interaction due to albumin binding should be limited since this binding is not saturable.

In vitro studies have been performed to determine whether elafibranor (GFT505) and it principal metabolite GFT1007 are substrates and/or inhibitors of major drug transporters, in order to assess the potential for drug-drug interaction (DDI). Based on the results of the OATP1B3 transporter inhibition assay, elafibranor (GFT505) has recently been assessed in a follow-up clinical DDI study with the OATP1B3-sensitive substrate, atorvastatin.

For the other drug transporters studied, the interaction observed does not require follow-up studies based on current regulatory guidance.

The metabolic stability and metabolism pathways of elafibranor (GFT505) have been studied on liver microsomes and in primary hepatocytes from rat, dog, mouse, monkey, and human. There was no evidence of the formation of unique human metabolites or metabolites formed at disproportionately higher levels in human hepatocytes than in any other species.

An in vivo study has been performed to compare the bioavailability of ^{14}C-GFT505 in the rat, dog, minipig, and monkey. This study showed that in all species ^{14}C-GFT505 is rapidly absorbed, although absolute bioavailability was moderate (about 20% to 40%).

1.4.4. Toxicology

1.4.4.1. Mutagenicity and genotoxicity

The toxicology program performed according to International Council for Harmonisation (ICH) guidelines demonstrates that elafibranor has no genotoxic or mutagenicity potential.

1.4.4.2. Acute toxicity

According to acute toxicity studies results, it can be concluded that elafibranor is extremely safe when administered as single oral doses in rat and mouse, since no sign of toxicity was detected up to the dose of 1000 mg/kg.

1.4.4.3. Repeated dose toxicity studies

The safety of elafibranor has been assessed in multiple preclinical toxicology studies with repeated-dose oral administration for up to 6 months in rats and 12 months in monkeys. Moreover, two-year repeated-dose carcinogenicity studies in mice and rats have been completed.

The only consistent safety concern raised by these studies is the expected PPARα-associated hepatomegaly, hepatocellular hypertrophy, and liver carcinoma in rodent species (mice and rats). However, it is well known that, compared to nonhuman primates and humans, rodents are highly sensitive to PPARα agonist induced peroxisome proliferation and associated liver side effects. Thus, available information on this class of drug which includes marketed fibrates together with the lack of any liver side effects in monkeys treated with high doses of elafibranor for 1 year support the nonrelevance to human.[19] Overall, these studies did not reveal any other safety issues up to the highest doses tested. Notably, elafibranor did not have any of the known PPARγ-related concerns such as excess in weight gain, hemodilution, edema, cardiomegaly, adiponectin induction, or urinary bladder carcinoma.

1.4.4.4. Phototoxicity studies

The phototoxic potential of elafibranor has been assessed by the in vitro 3T3 NRU phototoxicity test and the UV- Local Lymph Node Assay (LLNA) test in mice. Elafibranor (GFT505), but not its major metabolite GFT1007, showed UVA-dependent cytotoxicity in vitro. The UV-LLNA test was performed in mice with oral dosing for 3 days at up to 800 mg/kg/day elafibranor. Although a very conservative no observed effect level (NOAEL) was set at 400 mg/kg/day based on isolated findings at the highest dose, it is considered that data are more in favor of an absence of phototoxic effect, given the tissue distribution of elafibranor (GFT505), and absence of phototoxicity signal in the clinical studies.

1.5. CLINICAL STUDIES

1.5.1. NASH

A Phase I program to assess the safety and tolerability as well as the PK profile of elafibranor has been conducted through 12 completed clinical trials, and 5 still ongoing. A total of 561 healthy lean subjects, 60 overweight or obese subjects, and 12 patients with type 2 diabetes, 6 with end stage renal disease and 20 with hepatic impairment (Child-Pugh class A, B or C) have been randomized to date in the completed trials. Elafibranor daily doses ranged between 5 mg and 360 mg, with a treatment duration up to 16 days.

A Phase 2 program was initiated to assess the safety and efficacy profile of elafibranor in subjects with cardiometabolic disorders and NASH. To date, 5 Phase 2a studies have been completed, in which 297 subjects were randomized: 37 with mixed hyperlipidemia (type IIb Frederickson); 94 with atherogenic dyslipidemia and abdominal obesity; 47 with impaired glucose tolerance and abdominal obesity; 97 with diabetes mellitus type II; and 22 with insulin resistance and abdominal obesity. A Phase 2b study has also been completed, in which 274 subjects with NASH were randomized. In the Phase 2 program, the elafibranor daily doses ranged between 30 mg and 120 mg, with a maximum treatment duration of 12 months.

A Phase 2a randomized, open-label, sequential cohort study (GFT505E-218-1) will assess the PK and pharmacodynamic (PD) profile and the safety and tolerability of two dose levels of GFT505 (80 mg and 120 mg) in children and adolescents, 8 to 17 years of age, with NASH. In this study, subjects will receive 80 or 120 mg of GFT505 once daily for 12 weeks. The study consists of two paediatric patient cohorts with NASH which will be dosed sequentially. Cohort 1 will consist of +/- 12 subjects who are ≥12 to ≤17 years of age. Once 10 subjects in cohort 1 have been evaluated for PK and safety through Visit 4 (30 days) by an independent Data Safety Monitoring Board (DSMB), enrollment will be open to subjects ≥8 to ≤11 years of age. Cohort 2 will consist of +/- 8 subjects who are ≥8 to ≤11 years of age.

At time of DSUR data lock point (31 July 2019), 1 subject (≥12 to ≤17 years of age) had been enrolled and exposed to at least one administration of GFT505.

A Phase 2 study (GFT505-219-8) to evaluate the effect of a 6-week elafibranor (120 mg) treatment administered once daily on hepatic lipid composition in subjects with nonalcoholic fatty liver (NAFL) is currently ongoing. This study intends to achieve mechanistic information about the mode of action of elafibranor on the (lipid) metabolism in the human fatty liver. Subjects with NAFL will receive 120 mg of GFT505 or placebo once daily for 6 weeks in randomized order in a crossover design. Overall, 16 subjects with NAFL are intended to be included.

For additional information see Investigator's Brochure.

1.5.2. PBC

Based on the mechanism of action of elafibranor, and on the relevant efficacy and safety data collected to date, specifically on decrease in ALP and inflammation markers, a Phase 2a study has been launched in PBC has been completed, under IND 132202, filed in September 2016. The aim of this study was to validate the efficacy of elafibranor on ALP decrease in this patient population, and to confirm its safety in a population with PBC. This study was designed to compare the effect of daily oral administration for 12 weeks of GFT505 80 mg and 120 mg on changes in serum alkaline phosphatase (ALP) to that of placebo in subjects with PBC and inadequate response to ursodeoxycholic acid (UDCA).

For additional information see Investigator's Brochure.

1.6. CONCLUSION

Clinical data confirmed the beneficial effect of elafibranor in NASH patients, with efficacy on histology associated with improvement on insulin resistance, and with relevant reductions in markers of liver injury such as GGT and ALT, and in inflammatory markers. It demonstrated also improvement in lipid profile resulting in a beneficial balance between pro and anti-atherogenic markers.

Moreover at the last DSUR cut-off date (31 July 2019), 25 clinical studies with elafibranor have been conducted or are ongoing (in which a total of 3245 subjects have been randomized, including an estimated 2206 subjects exposed to elafibranor. In general, the treatment was well tolerated. No interaction, medication errors, or abuse/misuse cases have been reported to this date. See Section 6.6 for further information.

For additional information see Investigator's Brochure.

1.7. RATIONALE FOR STUDY POPULATION

Given the natural fluctuation of the disease for patients with mild NASH (NAS score of 3), phase IIb study results have clearly highlighted that only NASH patients with moderate to severe disease (NAS score≥4) should be treated.

Regarding fibrosis, available data from meta-analyses demonstrate that NASH patients are at greatest risk of progression to advanced fibrosis, cirrhosis, and liver outcomes. Patients with NASH develop progressive fibrosis in 25% to 50% of individuals over 4-6 years, while 15% to 25% of individuals with NASH can progress to cirrhosis.[20] In another study, with a mean follow-up of 13 years, 13.3% of NASH patients with mild to moderate fibrosis (stage 1-2) and 50% of patients with fibrosis stage 3 at inclusion developed cirrhosis.[21]

Considering these data, it is reasonable to include NASH patients with any stage of fibrosis (stage 1 to 3) in the Phase III program, from both safety and prospect for benefit standpoints. However, since in patients with NASH and advanced fibrosis (F2-F3) the probability of developing cirrhosis is much higher than in patients with early fibrosis (F1), the population evaluated for the long-term outcome needs to be based on the advanced fibrosis patients in order to enhance the chances of demonstrating a benefit within a reasonable timeframe.

Accordingly, the target population for the analysis of surrogate endpoint and liver outcomes will be NASH patients with advanced fibrosis (F2-F3). The enrollment of patients with advanced fibrosis for the evaluation of long-term outcomes including progression to cirrhosis should ensure that an expected number of events, calculated based on progression rate for each fibrosis stage, are obtained. Based on the literature,[21,22,23,24,25] in patients with NASH and advanced fibrosis (F2-F3) this progression rate can be estimated at 8% per year for fibrosis stage 3 and 6% per year for fibrosis stage 2, thus an average of 7% for advanced fibrosis.

As a conservative approach, no supplementary percentage was added to the estimated progression rate to histological cirrhosis (7%) for all the other events of the composite endpoint not linked to cirrhosis. Generally, liver decompensation events occur only when cirrhosis is present and the progression rate to the other events is expected to be very low.

A limited number of NASH patients with fibrosis stage 1 and associated comorbidities known to be at risk of fast disease progression will be included in the study as an exploratory group.

Enrollment of female patients will be capped at 40% in each group for this study to mirror the higher prevalence of NASH in males compared to females.[26]

1.8. JUSTIFICATION OF THE SELECTED DOSE

The results obtained in the Phase IIb study evaluating the resolution of NASH clearly demonstrated the superiority of the elafibranor dose of 120 mg over 80 mg on the histological endpoint, regardless of the population selected (Intent-To-Treat [ITT] or Full Analysis Set) or the subgroup tested, indicating that the dose to be used for the Phase III trial should be 120 mg.

To support this assumption, a dose-response modeling was performed based on data obtained in the Phase I clinical program with 14-day repeated dose studies ranging from 5 mg to 360 mg daily dose. In this model, the studied response was the change at endpoint versus baseline in biochemical parameters known to be associated in a dose-dependent manner with elafibranor exposure, such as liver enzymes (ALT, GGT, alkaline phosphatase), plasma lipids (triglycerides, LDL-C, HDL-C) or serum creatinine. Based on this modeling, the optimum dose was consistently assessed as a value of 118 mg. Therefore, given its good safety profile and evidence of efficacy, both supported by the dose-response modeling, 120 mg elafibranor appears to be the most appropriate dose for the upcoming Phase III trial.

1.9. RATIONALE FOR EFFICACY ENDPOINT

1.9.1. Primary endpoint for application under conditional approval

Steatohepatitis is indirectly associated with reduced hepatic survival in NAFLD.[21,27] It drives fibrogenesis, a slow process of hepatic scar formation that can result in cirrhosis and its deadly complications such as liver failure, portal hypertension, and hepatocellular carcinoma. Consequently, clearance of steatohepatitis,[28] i.e., reversal to a normal liver or to steatosis without steatohepatitis – a condition not associated with increased hepatic morbidity or mortality – is expected to improve hepatic prognosis. Natural history studies are now available showing that patients with steatohepatitis but not those with steatosis only (i.e., nonNASH NAFLD) are the ones that progress to cirrhosis and liver-related outcomes. This forms the basis for "resolution of NASH" as a desirable outcome of therapy in the short-term; a concept widely embraced by the academic community and expressed in several scientific society endorsed position papers.[29,30] Based on the recently published recommendations from this workshop,[30] resolution of NASH with no worsening of fibrosis may be an acceptable surrogate endpoint suitable for a Phase III enrolling patients with NASH and fibrosis. Based

on recent data that have shown that fibrosis stage of 2 or more is related to liver-related mortality,[22] the "no worsening of fibrosis" should be no progression of one stage in fibrosis.

1.9.2. Primary endpoint for clinical outcome (postapproval confirmation)

The primary endpoint of the Long-term Treatment Period (LTTP) of the study is to evaluate the effect of elafibranor on the progression to cirrhosis, all-cause mortality, and liver-related clinical outcomes as measured by the onset of any of the listed adjudicated events (clinical outcomes composite endpoint).

Primary endpoint events include overall mortality, progression to cirrhosis, and the full list of portal hypertension/cirrhosis related events (liver transplantation, model end stage liver disease (MELD) score ≥15, hepatocellular carcinoma (HCC), and hospitalization due to occurrence of hepatic encephalopathy, variceal bleeding, spontaneous bacterial peritonitis, uncontrolled ascites, hepatorenal syndrome, hepatopulmonary syndrome, and chronic gastrointestinal blood loss due to portal hypertensive gastropathy [provided that these lead to hospitalization or transfusion]).

Singh et al. recently provided a thorough meta-analysis of paired biopsy studies to obtain the most accurate estimate of the fibrosis progression rate in a large cohort of patients with NAFLD.[25] Over 2145.5 person-years of follow-up evaluation, 33.6% had fibrosis progression, 43.1% had stable fibrosis, and 22.3% had an improvement in fibrosis stage. Overall, the annual fibrosis progression rate in a population of patients with NAFLD who had stage 0 fibrosis at baseline was 0.07 stage/year compared to 0.14 stage/year in a population of patients with NASH. In another study of 108 patients, no significant difference in the proportion exhibiting fibrosis progression was found between those with NAFLD or NASH.[31] In the whole cohort, the mean annual rate of fibrosis progression was 0.08 stage/year.

Based on the literature, in patients with NASH and advanced fibrosis (F2-F3), the probability of developing cirrhosis can be estimated at 8% per year for fibrosis F3 and 6% per year for fibrosis F2.[21,22,23,24,25]

In conclusion, the difference in progression to cirrhosis, other liver-related events, and total deaths between treatment and control groups can be considered as a potential clinically meaningful outcome measure for clinical trials. This long-term outcome including progression to cirrhosis is considered acceptable,[30] and required in a postapproval study for treatments approved under conditional approval.

1.10. RATIONALE FOR STUDY DURATION

In accordance with the AASLD and EASL recommendations, 72-weeks of treatment have been defined for the first stage of the study in order to demonstrate the efficacy of elafibranor on resolution of NASH without worsening of fibrosis.

The estimated duration of the LTTP is based on a 7% probability of patients with NASH and moderate and advanced fibrosis (F2-F3) developing cirrhosis or other liver-related events as determined from recently published data [21,22,23,24,25] and the available data of the mortality risk in this patient population.[32,33]

1.11. RATIONALE FOR SAFETY MONITORING

The safety of use of the dose of 120 mg/d of elafibranor during the proposed trial is supported by the chronic toxicity studies and previous Phase I and Phase II trials. Indeed, the toxicology package of elafibranor does not reveal any major safety concern, based on the conclusion that elafibranor-induced liver toxicity in rodents is not relevant to nonprimates (no evidence of liver toxicity in monkeys after 1 year but improvement of liver function markers) and humans (consistent improvement of liver function markers in all Phase II trials). These toxicology results and conclusions are on-line with the extensive literature on the liver effects of PPAR agonists.

An independent DSMB will be established in order to review the progress of the study and to perform a safety data review (as defined by the DSMB Charter) on a regular basis during the trial to protect patient welfare and preserve study integrity.

Knowing the risks associated with NASH and disease progression, specific attention will be paid to potential hepatotoxicity, liver-related and cardiovascular events.

Given the known effect of elafibranor on serum creatinine increase, special attention will be paid to all the renal safety markers (plasmatic or urinary parameters), including but not limited to albumin-creatinine ratio, cystatin C, neutrophil gelatinase-associated lipocalin (N-Gal), N acetyl β D-glucosaminidase β-NAG, kidney injury molecule-1 (KIM-1). Serum creatinine, modification of diet in renal disease (MDRD) derived estimated glomerular filtration rate (eGFR), and the results of urinalysis (dipstick) will be reported at each visit, as well as blood urea nitrogen. The other markers (plasmatic or urinary) will be assayed in batch and will be reviewed on an ongoing basis through regular safety reviews by the DSMB which includes a nephrologist.

Assays of many other markers are scheduled in order to monitor liver function markers, cardiac safety markers, and to follow up the cardiovascular profile which is known to be at risk in NASH patients.

For cardiac safety, troponin-T and NT-ProBNP will be followed and reviewed on a regular basis by the DSMB. In addition, electrocardiogram (ECG) and blood pressure (BP) will be routinely monitored throughout the study.

Liver function will be monitored throughout the study, by assessment of liver enzymes, bilirubin (total and conjugated), alkaline phosphatase, and international normalized ratio (INR) reported at each visit.

In addition, even if no safety concern has been revealed in the previous clinical program, all the biological parameters that are known to be affected by PPAR agonists will remain monitored in the Phase III trials, such as hematological parameters, adiponectin, or homocysteine.

During the LTTP, patients will be monitored by clinical and biological assessment. A FibroScan® measurement and noninvasive markers assessment will be performed every 24 weeks, and if cirrhosis is suspected, a confirmation by liver biopsy will be performed.

For additional information see Investigator's Brochure.

2. TRIAL OBJECTIVES

To assess the efficacy and safety of elafibranor as compared to placebo in adult NASH patients with fibrosis stage 2 or 3 (F2-F3), the primary and secondary objectives are as follows:

2.1. PRIMARY OBJECTIVES

2.1.1. Surrogate endpoint analysis

To evaluate the efficacy of elafibranor 120 mg QD for 72 weeks versus placebo on resolution of NASH without worsening of fibrosis.

- Resolution of NASH is defined as the disappearance of ballooning and disappearance or persistence of minimal lobular inflammation (grade 0 or 1) with an overall pattern of injury not qualifying for steatohepatitis.
- Worsening of fibrosis is evaluated using the NASH Clinical Research Network (CRN) fibrosis staging system and defined as progression of at least 1 stage.

2.1.2. Long-term endpoint

To evaluate the efficacy of elafibranor 120 mg QD versus placebo on clinical outcomes described as a composite endpoint composed of death due to any cause, histological liver cirrhosis, and the full list of portal hypertension/cirrhosis related events:

- Liver transplantation
- MELD score ≥15
- HCC
- the onset of:
    - variceal bleed
    - hepatic encephalopathy
    - spontaneous bacterial peritonitis
    - ascites
    - hepatorenal syndrome
    - hepatopulmonary syndrome
    - chronic gastrointestinal blood loss due to portal hypertensive gastropathy (provided that these lead to hospitalization or transfusion).

2.2. KEY SECONDARY OBJECTIVES – AT SURROGATE ENDPOINT ANALYSIS

To assess histological changes after 72 weeks of treatment, at the time of surrogate endpoint analysis, on the following endpoint:

- Percentage of patients with improvement of fibrosis of at least 1 stage according to NASH CRN scoring.

To assess the clinical benefit after 72 weeks of treatment on the following metabolic endpoints:

- Changes from baseline in triglycerides, Non-HDL cholesterol, HDL cholesterol, LDL cholesterol, HbA1c (in diabetic patients), HOMA-IR (in non-diabetic patients)

2.3. OTHER SECONDARY OBJECTIVES

- To assess histological changes after 72 weeks of treatment and at the end of the LTTP on the following endpoints:
    - percentage of patients with resolution of NASH without worsening of fibrosis (at the end of LTTP)
    - percentage of patients with improvement of fibrosis of at least 1 stage according to NASH CRN scoring (at the end of LTTP)
    - percentage of patients with improvement of fibrosis of at least 1 stage according to NASH CRN scoring without worsening of NASH
    - percentage of patients with no worsening of fibrosis and no worsening of NASH
    - percentage of patients with resolution of NASH and improvement of Fibrosis
    - percentage of patients with at least a 1 point improvement in histological scores (NASH CRN scoring: NAS [sum of steatosis, hepatic ballooning and lobular inflammation], steatosis, hepatic ballooning, lobular inflammation), fibrosis (NAFLD Ishak scoring system), or portal inflammation
    - percentage of patients with improvement of NAS of at least 2 points
    - percentage of patients with improvement of NAS of at least 2 points and with at least 1 point improvement in hepatic ballooning
    - percentage of patients with at least a 1 point improvement in disease activity score (sum of ballooning and lobular inflammation scores) according to NAS scoring and steatosis-activity-fibrosis (SAF) scoring
    - percentage of patients with at least a 1 point improvement in disease activity score (sum of ballooning and lobular inflammation scores) according to NAS scoring and with at least 1 point improvement in hepatic ballooning
    - percentage of patients with at least a 1 point improvement in disease activity score (sum of ballooning and lobular inflammation scores) according to SAF scoring and with at least 1 point improvement in hepatic ballooning
    - percentage of patients with at least 2 points improvement in disease activity score according to NAS scoring and SAF scoring
    - changes in NAS, fibrosis (using NASH CRN and NAFLD Ishak scoring system), steatosis, hepatic ballooning, lobular inflammation, portal inflammation and SAF activity score

  - changes in area of fibrosis (normalized Collagen Proportional area in %) by morphometry
- To assess the following endpoints at Week 72 and at the end of the LTTP:
  - changes in liver enzymes and liver markers
  - changes in noninvasive markers of fibrosis and steatosis
  - changes in lipid parameters
  - variation in body weight
  - changes in insulin resistance and glucose homeostasis markers
  - changes in inflammatory markers
  - changes in cardiovascular risk profile as assessed by Framingham scores
  - changes in liver stiffness by Fibroscan measurement
  - changes in quality of life (36-Item Short-Form Health Survey [SF-36] questionnaire).
- To assess the onset to:
  - histological liver cirrhosis
  - death of any cause
  - any portal hypertension or cirrhosis related events
  - cardiovascular events
  - liver-related death events

2.4. EXPLORATORY OBJECTIVES

- To constitute a biobank for discovery and validation of biomarkers in NASH.

2.5. EXPLORATORY OBJECTIVES FOR F1 GROUP AND THE OVERALL POPULATION (WHATEVER THE FIBROSIS STAGE – F1, F2 OR F3)

- To explore, in F1 patients and in the overall population whatever the fibrosis stage (F1, F2 or F3), the same endpoints as for the primary and secondary objectives.

2.6. SAFETY SECONDARY OBJECTIVES

To assess the tolerability and safety of once a day administration of oral doses of elafibranor 120 mg:

- SAE, AE, physical examination, vital signs, medical history, ECG
- hematological parameters
- liver markers
- renal biomarkers (including urinalysis)
- cardiac biomarkers
- metabolic parameters
- other biochemical safety markers.

3. TRIAL DESIGN

This is a Phase III, randomized, double-blind, parallel groups, placebo-controlled study, evaluating the efficacy and safety of elafibranor 120 mg QD versus placebo in an adult NASH population with fibrosis.

The first double-blind 72-week Treatment Period will assess the efficacy and safety of elafibranor on the resolution of NASH without worsening of fibrosis at the surrogate endpoint efficacy analysis, followed by a LTTP to assess efficacy on progression to cirrhosis, all-cause mortality, and liver-related clinical outcomes as measured by the onset of any of the listed adjudicated events (see Section 2.1.2). The study will terminate upon the 456th patient (excluding exploratory F1 group [see below]) experiencing an event listed in the composite endpoint for long term efficacy evaluation.

It is planned to randomize patients to either active or placebo treatment in a 2:1 ratio, stratified by type 2 diabetes, gender (with a capping of women to 40%), and fibrosis stage. Additional patients with fibrosis stage 1 (10% of sample size calculated for the F2 and F3 patients) and high risk for progression of NASH will also be enrolled for exploratory purposes.

3.1. NUMBER OF PATIENTS

It is planned to randomize at least 2022 F2/F3 patients to either active (1348 patients) or placebo (674 patients) treatment in a 2:1 ratio. Up to 202 additional patients (a maximum level of 10% of the F2/F3 enrolled patients) with fibrosis stage of 1 and high risk for progression of NASH (NAS ≥5, F1 patients with at least 2 of the following conditions: persistent elevated (absence of normal ALT within the past year, obesity defined by a body mass index (BMI) ≥30, metabolic syndrome [National Cholesterol Education Program's Adult Treatment Panel III {NCEP ATP III definition}], type 2 diabetes, or HOMA-IR >6) will also be enrolled, and followed as an exploratory group. The F1 patients will not be included in the primary surrogate endpoint and final analysis or in the sample size calculation (detailed in Section 9.7). As such a total of at least 2224 patients will be enrolled, including the exploratory F1 group.

3.2. METHOD OF ASSIGNING PATIENT TO TREATMENT GROUP

Patients who satisfy all eligibility criteria will be randomly allocated to one of the following groups in a 2:1 ratio:

- Elafibranor 120 mg
- Placebo.

Randomization to treatment will be stratified to ensure balance of treatment allocation by the following 3 factors:

- Type 2 diabetes (yes, no)

- Gender (male, female) (with a capping of women to 40%)
- Fibrosis stage (F1, F2, F3) (capped to 202 F1 patients).

Treatment assignments will be made using an interactive voice/web response system (IXRS).

3.3. DOSE ADJUSTMENT CRITERIA

Not applicable. Patients will be randomized to a fixed dose with no allowance for dose adjustment.

3.4. DURATION OF STUDY PARTICIPATION

The estimated duration of the study will be approximately 96 months, based on 456 patients experiencing an event described in Section 2.1.2 at an assumed annual rate event of 7%. However, this may be redefined according to the actual occurrence of events (described in Section 2.1.2) during the confirmatory part of the study (LTTP).

3.5. STUDY PERIODS

The study will comprise 3 periods. The Screening Period (-12 to -1 weeks) will precede a 72-week double-blind First Treatment Period and a LTTP up to the occurrence of a prespecified number of events.

Study procedures are summarized in Table 1, Table 2, and Figure 1.

Schedule:

- Week -12 to Week -1 prior to Randomization: Screening Period (screening visits SV1 to SPV).
- Week 0 to Week 72: First Treatment Period with Elafibranor or placebo for 72 weeks (visits V1 to V7).
- Week 72 to end of study (EOS): LTTP with elafibranor or placebo until 456 patients experience an event listed in Section 2.1.2 (visits V8 to Vn).

3.6. SCREENING PERIOD (WEEK -12 TO WEEK -1)

3.6.1. Screening visits SV1 and SV2

The following screening procedures will be performed for all potential patients at SV1 conducted during the screening period and prior to randomization:

- Signature of informed consent witnessed by the Investigator or designated person. **Note**: The signature of the informed consent may also be performed before SV1.
- Patient number allocation via IXRS.
- Check medical history/demographics.
- Check inclusion/exclusion criteria (described in Section 4).
- Physical examination (described in Section 6.2.1).

- Adequate diet recommendations (described in Section 5.1.1 and APPENDIX II: Adequate diet and lifestyle recommendations), alcohol restrictions (described in Section 5.1.2), and tobacco habits.
- Record vital signs (described in Section 6.2.3).
- Record height, weight, and waist circumference.
- Check concomitant/prior medication (within 6 months prior to Screening) (described in Section 7.12 and APPENDIX III: Permitted/non-permitted medication)
- Check if a liver biopsy with confirmed NASH and fibrosis is available, and, if so send sample for central confirmation of NASH diagnosis (described in Section 6.1.1.2). This historical diagnostic biopsy should be obtained within 6 months prior to the Screening Visit.
- Check AEs from time of Informed Consent Form (ICF) signature (described in Section 6 and Section 8).

The Screening biological assessment (SB1 will be scheduled at SV1).

If no diagnostic liver biopsy (within 6 months of SV1) is available, it is recommended to schedule an additional SV2 visit at least Week -4 prior to the planned Randomization V1, in order to obtain the results in time.

The following biological assessments (detailed in Table 2) will be performed at SB1:

- Blood samples (described in Table 2).
- Whole blood, plasma & serum bank samples (only if additional genetic and biomarker ICF signed).
- Urinalysis dipstick.
- Urinary pregnancy test (for women of childbearing potential only [WOCBP]).

If no historical values of AST, ALT, total bilirubin and INR meeting the requirements of within 8 weeks to 6 months of randomization visit are available, then SV1 and V1 must be scheduled at least 8 weeks apart in order to have 2 consecutive values for DILI adjudication.

In case of known cured hepatitis C virus (HCV) infection, HCV RNA testing can be done at SV1 without waiting for HCV Ab results.

If needed, a retesting of abnormal HbA1c, or creatine phosphokinase (CPK) results or additional testing of HCV RNA, may be performed during the screening window to determine the eligibility for the study as described in exclusion criteria 5, 12, 30, and 31 (see Section 4.2 and Section 3.11).

At visit SV1, preliminary entrance criteria will be reviewed. Potentially eligible patients will be asked if they agree to participate in the study and sign the ICF. Each patient who has signed the ICF will be allocated a patient number composed of 9 digits which is generated by the IXRS.

- First 3 digits corresponding to the ISO numeric country code (this number will be predefined),
- Next 3 digits corresponding to the site number (this number will be predefined),
- Last 3 digits corresponding to the numerical order of the patient entry at the study site.

A specific IXRS procedure manual will be provided to the Investigator.

3.6.2. Screening Visit SV2 (liver biopsy if required, Week -12 to recommended Week -4):

If no diagnostic liver biopsy within 6 months of SV1 is available, it is recommended to schedule an additional SV2 visit at least Week -4 for a liver biopsy to be performed (described in Section 6.1.1.1). Blood samples for coagulation (detailed in Table 2) will be taken and tested at a local laboratory prior to the liver biopsy. Liver biopsy samples will be sent for central confirmation of NASH diagnosis (described in Section 6.1.1.2).

During this visit AEs (from the time of signing the ICF) will also be checked (described in Section 6 and Section 8).

3.6.3. Screening Phone Visit SPV (Week -1):

Upon receipt of the NASH diagnosis confirmation and the SB1 or any retesting/additional testing results from the central laboratory, the Investigator should check the eligibility with inclusion/exclusion criteria.

If patient meets all inclusion criteria and none of the exclusion criteria (clinical, histological, and biological ones), the Investigator will inform the patient of his/her inclusion/noninclusion status by a phone call within 1 week prior to the Randomization Visit V1. In case of ineligibility, the patient should be contacted as soon as possible.

3.7. FIRST TREATMENT PERIOD (WEEK 0 TO WEEK 72)

Efficacy of elafibranor versus placebo on resolution of NASH without worsening of fibrosis will be evaluated in this first period treatment of 72 weeks.

The NASH will be evaluated for inclusion by a centrally-read liver biopsy taken within 6 months prior to Screening (if no historical biopsy is available for NASH diagnosis, a liver biopsy will be performed during the Screening Period) with:

- Presence of NASH, with at least a score of 1 in each component of the NAS (steatosis scored 0 to 3, ballooning degeneration scored 0 to 2, and lobular inflammation scored 0 to 3) AND NAS ≥4.
- Fibrosis stage 2 and 3.

A group of patients (n=202, 10% of each group) with F1 fibrosis, NAS ≥5, and concomitant cardiometabolic comorbidities, which are associated with rapid progression of the disease (listed in Section 3.1), will also be enrolled and followed as an exploratory group.

During these first 72 weeks of treatment, visits will be scheduled every 12 weeks. Clinical and biological evaluation will be performed during this First Treatment Period.

At the end of the 72-week treatment period, a biopsy will be performed for all the patients under treatment in order to evaluate the effect of elafibranor on the liver histology.

When at least the first 1023 randomized patients (F2-F3) complete Week 72 (or discontinue early from the study treatment), a surrogate endpoint analysis will be performed and potentially filed for initial market approval under Subpart H or conditional approval, (see Section 9.8.1 for details).

During the First Treatment Period the patients will return to the site for visits every 12 weeks (±1 week) from the Randomization Visit (V1); however the maximum time period between visits is to be 96 days due to the study drug supply provided to the patient.

A diagnosis of any event listed in the primary composite endpoint described in Section 1.9.2 will result in the permanent discontinuation of study drug and discontinuation from the study, following an end of study treatment (EOT) Visit as described in Section 3.9 and Section 5.2.2).

3.7.1. Randomization Visit V1 (Week 0):

Eligible patients will return to the site at the Randomization Visit V1 and then every 12 weeks in the First Treatment Period of the study until the first 72 weeks of treatment (V7) (surrogate endpoint analysis). The patient will be contacted at least 1 week before each visit to be reminded of procedures and investigational product (IP) return.

If the patient is eligible, the Investigator will register the patient for randomization in the IXRS, prior to any other study procedures. If the system confirms the randomization, it will provide the Investigator with a treatment number for the patient.

The following will be performed only at V1:

- Check inclusion/exclusion criteria (detailed in Section 4).
- Randomization to one of 2 treatments groups (elafibranor or placebo in 2:1 ratio, detailed in Section 3.2) via the IXRS.

3.7.2. First Treatment Period visits V1 to V7 (Week 0 to Week 72):

The following procedures will be performed at each of the 12-week visits from V1 to V7:

- IXRS registration
- Physical examination (described in Section 6.2.1)
- Record vital signs and weight (described in Section 6.2.1 and Section 6.2.3)
- Confirmation of adequate diet and lifestyle compliance (described in Section 5.1.1 and APPENDIX II: Adequate diet and lifestyle recommendations), alcohol restrictions (described in Section 5.1.2), and tobacco habits

- Check concomitant/prior medication (described in Section 7.12 and APPENDIX III: Permitted/non-permitted medication)
- Quality of life assessment (V1, V3, V5, and V7, only; described in Section 6.2.6)
- Check AEs (all visits) and occurrence of any clinical outcome (from V2 onwards) (described in Section 6 and Section 8)
- Study placebo or drug dispensation (described in Section 7.6)
- Blood samples (described in Table 2)
- Plasma & serum bank samples (only if additional genetic and biomarker ICF signed)
- Urinalysis and urinary dipstick (described in Table 2)
- Urinary pregnancy test (for WOCBP only)
- Provision of home pregnancy test kits (for WOCBP only)
- Record result of home pregnancy tests (to be performed every 4 weeks [see Figure 2]) since previous visit (for WOCBP only, every visit from V1)
- Record waist circumference (V1, V3, V5, and V7, only)
- 12-lead ECG (V1, V4, and V7, only; described in Section 6.2.4)
- FibroScan (V1 and V7 only, described in Section 6.2.5)
- Drug accountability (every visit from V2).

Additional procedures to be performed at V7 are:

- Liver biopsy (described in Section 6.1.1). **Note:** the liver biopsy may be performed at V7 or during a separate visit that occurs within the V7 window of 72 weeks ± 1 week from V1. Liver biopsy samples will be sent for central histological evaluation.
- Blood samples for coagulation taken (platelets count and prothrombin time [PT (INR)]; described in Table 2) and tested at a local laboratory prior to the liver biopsy.

3.8. LONG-TERM TREATMENT PERIOD

The main objective to be evaluated during the LTTP will be the prevention of progression to cirrhosis, death due to any cause, or to portal hypertension/cirrhosis related events (as described in Section 1.9.2).

After the 72-week biopsy, patients will continue in the double-blind LTTP, receiving the same treatment as assigned at V1 (elafibranor 120 mg or placebo). Patients will be monitored by notably measuring the appearance of cirrhosis (based on FibroScan measurement associated with biological and/or clinical assessments and confirmed by biopsy).

At or after the 72-week biopsy, a diagnosis of any event listed in the primary composite endpoint described in Section 1.9.2 will result in the permanent discontinuation of study drug and discontinuation of the study following the EOT Visit (as described in Section 3.9 and Section 5.2.3).

3.8.1. Long-term Treatment Period visits (V8 to Vn)

Patients will return to the site every 24 weeks during the LTTP. The patient will be contacted at least 1 week before each visit to be reminded of procedures and IP return.

The following procedures will be performed at each visit from V8 to Vn:

- IXRS registration
- Physical examination (described in Section 6.2.1)
- Record vital signs and weight (described in Section 6.2.1 and Section 6.2.3)
- Confirmation of adequate diet and lifestyle compliance (described in Section 5.1.1 and APPENDIX II: Adequate diet and lifestyle recommendations), alcohol restrictions (described in Section 5.1.2), and tobacco habits
- Check concomitant/prior medication (described in Section 7.12 and APPENDIX III: Permitted/non-permitted medication)
- Quality of life assessment (V8, V9, V11, and every 48 weeks thereafter Section 6.2.6)
- Check AEs and occurrence of any clinical outcome (described in Section 6 and Section 8)
- Study placebo or drug dispensation (described in Section 7.6)
- Blood samples (described in Table 2)
- Plasma & serum bank samples (only if additional genetic and biomarker ICF informed consent signed)
- Urinalysis and urinary dipstick (described in Table 2)
- Urinary pregnancy test (for WOCBP only)
- Provision of home pregnancy test kits (for WOCBP only)
- Record result of home pregnancy tests (to be performed every 4 weeks [see Figure 2]) since previous visit (for WOCBP only, every visit from V1)
- Record waist circumference
- 12-lead ECG (every 48 weeks from V9; described in Section 6.2.4)
- FibroScan (described in Section 6.2.5)
- Drug accountability
- Liver biopsy (at approximately 4 years [V13], and in case of suspected liver cirrhosis, described in Section 6.1.1). Liver biopsy samples will be sent for central histological evaluation
- Blood samples for coagulation taken (platelets count and PT [INR]; described in Table 2) and tested at a local laboratory prior to the liver biopsy.

3.8.2. Long-term Treatment Period phone visits (PV1 to PVn)

Phone visits will be scheduled every 24 weeks starting 12 weeks after Visit 7 for data collection on diet and lifestyle, concomitant medications, clinical outcomes, safety, home pregnancy test results, and IP compliance control. If any information during this phone contact requires a visit, the Investigator may decide to perform an unscheduled visit (described in Section 3.11.2). IXRS registration will be performed for each phone visit.

3.9. END OF STUDY TREATMENT VISIT

At the EOS (upon occurrence of the expected number of events), all patients will be asked to stop treatment and undergo an EOT Visit 30 days after the final administration of study drug.

All patients who permanently discontinue their study medication will undergo an EOT Visit 30 days after the final administration of study drug. Patients who permanently discontinue study drug for any reason other than an event listed in the primary composite endpoint for long-term efficacy described in Section 1.9.2 will remain, upon agreement, in the study after the EOT Visit and be followed up to evaluate efficacy outcomes and safety through phone call visits every 24 weeks as described in Section 3.10 and Section 5.2.

If a patient discontinues from the study, every attempt should be made to have the patient return to the site and complete the EOT Visit 30 days after the final administration of study drug. For details of the EOT Visit see Table 1, Table 2, Figure 1, and Figure 2.

The patient will be contacted at least 1 week before the visit to be reminded of procedures and IP return (if required). The following procedures will be performed at the EOT Visit:

- IXRS registration
- Physical examination (described in Section 6.2.1)
- Record vital signs and weight (described in Section 6.2.1 and Section 6.2.3)
- Confirmation of adequate diet and lifestyle compliance (described in Section 5.1.1 and APPENDIX II: Adequate diet and lifestyle recommendations), alcohol restrictions (described in Section 5.1.2), and tobacco habits
- Check concomitant/prior medication (described in Section 7.12 and APPENDIX III: Permitted/non-permitted medication)
- Quality of life assessment (described in Section 6.2.6)
- Check AEs and occurrence of any clinical outcome(described in Section 6 and Section 8)
- Blood samples (described in Table 2)
- Plasma & serum bank samples (only if additional genetic and biomarker ICF informed consent signed)
- Urinalysis and urinary dipstick (described in Table 2),
- Urinary pregnancy test (for WOCBP only)
- Record results of home pregnancy tests (to be performed every 4 weeks [see Figure 2]) since previous visit (for WOCBP only)
- Record waist circumference
- 12-lead ECG (described in Section 6.2.4)
- Drug accountability.

Patients discontinuing study drug or discontinuing the study will be asked to return all used and unused study treatments at the EOT Visit.

3.10. FOLLOW-UP FOR PATIENTS WHO HAVE PERMANENTLY DISCONTINUED STUDY DRUG

Patients who have permanently discontinued study drug due to an event listed in the primary composite endpoint for long-term efficacy described in Section 1.9.2 will be discontinued from the study following the EOT Visit and have no further follow-up.

Patients who have permanently discontinued study drug for any other reason will remain, upon agreement, in the study and will be followed up with phone visits every 24 weeks (±2 weeks from EOT Visit) following the EOT Visit to report safety, diagnosis of cirrhosis and occurrence of clinical outcomes (as listed below) including liver and cardiovascular events until EOS or the occurrence of an event listed in the primary composite endpoint for long-term efficacy (described in Section 1.9.2), whichever is sooner.

The following procedures will be performed during the follow-up phone visit for patients who have permanently discontinued study drug:

- IXRS registration.
- Reporting of safety information regarding:
  - any new AEs
  - resolution of previous AEs
  - change in severity of existing AEs
  - occurrence of any cardiovascular events
  - occurrence of diabetes (for patients not previously diagnosed with diabetes)
  - worsening of diabetes (for patients previously diagnosed with diabetes).
- Reporting of any change in diet and life style factors
- Reporting of any change (quantitative or qualitative) in therapies post study drug discontinuation
- Reporting of cirrhosis diagnosis (patient to be asked if they have had any histological confirmation of cirrhosis)
- Reporting of any of the following events (primary composite endpoint for long-term efficacy evaluation):
  - liver transplantation
  - MELD score ≥15
  - HCC
  - the onset of:
    - variceal bleed
    - hepatic encephalopathy
    - spontaneous bacterial peritonitis
    - ascites
    - hepatorenal syndrome
    - hepatopulmonary syndrome

- chronic gastrointestinal blood loss due to portal hypertensive gastropathy (provided that these lead to hospitalization or transfusion).

- death due to any cause.

3.11. OPTIONAL VISITS

3.11.1. Retesting screening visits

Upon receipt of results from biological assessment done at SV1, and in case a retesting or additional testing is needed according to the selection criteria, an additional visit will be scheduled according to the recommended timeframe for retesting.

Permitted retesting or additional testing in case of abnormal value at SV1 are:

- CPK: can be repeated prior to Randomization (V1) within 1 to 2 weeks after initial test.
- HCV RNA testing: in case positive HVC Ab test at SV1 required latest 2 weeks prior to Randomization (V1).
- HbA1c: can be repeated at the latest 2 weeks prior to Randomization (V1).

Any other retest deemed necessary by the Investigator should be discussed with the Study Medical Monitors.

3.11.2. Unscheduled visits

An unscheduled visit is defined as any visit to the study unit outside of the protocol-evaluation timepoints where the patient is seen by study unit personnel, e.g., when follow-up assessments are required for safety reasons or when repeat measurements are required out of the screening period (either to confirm a measurement or in case of errors, measuring device failure, etc).

Unscheduled visits will be needed for patients who may require further follow-up due to safety.

3.12. EXPLORATORY/ANCILLARY SUBSTUDY

Exploratory substudies might be performed during the study in sites that have the corresponding capability. Specific study documents will be prepared and Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and authority approvals shall be obtained when applicable.

4. PATIENT SELECTION

A patient will be eligible for the study only if all of the following criteria apply:

4.1. INCLUSION CRITERIA

Patients must meet all of the following inclusion criteria to be eligible for enrollment in the trial:

1. Males or females aged from 18 to 75 years inclusive at first Screening Visit.
2. Must provide signed written informed consent and agree to comply with the study protocol.
3. Females participating in this study must be of nonchildbearing potential or using highly efficient contraception for the full duration of the study and for 1 month after the end of treatment, as described below:
    - Cessation of menses for at least 12 months due to ovarian failure,
    - Surgical sterilization such as bilateral oopherectomy, hysterectomy, or medically documented ovarian failure
    - If requested by local IRB regulations and/or National laws, sexual abstinence may be considered adequate (the reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient)
    - Using a highly effective nonhormonal method of contraception (bilateral tubal occlusion, vasectomized partner, or intra-uterine device)
    - Double contraception with barrier AND highly effective hormonal method of contraception (oral, intravaginal, or transdermal combined estrogen and progestogen hormonal contraception associated with inhibition of ovulation; oral, injectable, or implantable progestogen-only hormonal contraception associated with inhibition of ovulation; or intrauterine hormone-releasing system). The hormonal contraception must be started at least 1 month prior to Randomization.
4. Histological confirmation of steatohepatitis on a diagnostic liver biopsy by central reading of the slides (biopsy obtained within 6 months prior to Screening or during the Screening Period) with at least 1 in each component of the NAS (steatosis scored 0-3, ballooning degeneration scored 0-2, and lobular inflammation scored 0-3).
5. NAS ≥4.
6. Fibrosis stage of 1 or greater and below 4, according to the NASH CRN fibrosis staging system.
   For patients with fibrosis stage 1, only patients at high risk of progression will be included meaning with a NAS ≥5 and at least 2 of the following conditions: persistent elevated ALT (absence of normal ALT within the past year), obesity defined by a BMI ≥30, metabolic syndrome (NCEP ATP III definition), type 2 diabetes, or HOMA-IR >6.
7. Patients in whom it is safe and practical to proceed with a liver biopsy, and who agree to have:

- 1 liver biopsy during the Screening Period for diagnostic purpose (if no historical biopsy within 6 months before screening is available)
- 1 liver biopsy after 72-weeks of treatment for assessment of the treatment effects on NASH
- a final liver biopsy after approximately 4 years of treatment (V13), unless a liver biopsy has already been performed within the past year
- 1 liver biopsy performed only in the case of suspicion of cirrhosis (to have a histological confirmation.

8. If a patient is treated with 1 of the following drugs: vitamin E (>400 IU/day), polyunsaturated fatty acids (>2 g/day), or UDCA; a stable dose from at least 6 months prior to diagnostic liver biopsy is required.
9. For patients with type 2 diabetes, glycemia must be controlled. If glycemia is controlled by antidiabetic drugs, change in anti-diabetic therapy must follow these requirements:
    - no qualitative change 6 months prior to diagnostic liver biopsy up to Randomization (i.e., implementation of a new anti-diabetic therapy) for patients treated with metformin, gliptins, sulfonylureas, sodium/glucose cotransporter (SGLT) 2 inhibitors, glucagon-like peptide (GLP)-1 agonists, or insulin. Dose changes of these medications are allowed in the 6 months prior to diagnostic liver biopsy, except for GLP-1 agonists, which must remain on stable dose in the 6 months prior to diagnostic liver biopsy.
    - no implementation of GLP-1 agonists and SGLT2 inhibitors up to 72 weeks of treatment (V7).

    Initiation of any other antidiabetic drugs is allowed after Randomization based on treating physicians' judgment, except for glitazones which are prohibited 6 months prior to diagnostic liver biopsy until the end of treatment.

4.2. EXCLUSION CRITERIA

Patients who meet any of the following criteria will be excluded from entering the study:

1. Known chronic heart failure (Grade I to IV of New York Heart Association classification).
2. History of efficient bariatric surgery within 5 years prior to Screening, or planned bariatric surgery in the course of the study.
3. Uncontrolled hypertension during the Screening Period despite optimal antihypertensive therapy.
4. Type 1 diabetes patients.
5. Patients with HbA1c >9.0%. If abnormal at the first Screening Visit, the HbA1c measurement can be repeated at the latest 2 weeks prior to Randomization. A repeated abnormal HbA1c (HbA1c >9.0%) leads to exclusion.
6. Patients receiving thiazoledinediones (glitazones [pioglitazone, rosiglitazone]), unless the drug was discontinued at least 6 months before the diagnostic liver biopsy.

7. Patients with a history of clinically significant acute cardiac event within 6 months prior to Screening such as: stroke, transient ischemic attack, or coronary heart disease (angina pectoris, myocardial infarction, revascularization procedures).
8. Weight loss of more than 5% within 6 months prior to Randomization.
9. Compensated and decompensated cirrhosis (clinical and/or histological evidence of cirrhosis). Notably, NASH patients with fibrosis stage = 4 according to the NASH CRN fibrosis staging system are excluded.
10. Current or recent history (<5 years) of significant alcohol consumption. For men, significant consumption is typically defined as higher than 30 g pure alcohol per day. For women, it is typically defined as higher than 20 g pure alcohol per day. See APPENDIX IV: Alcohol comparison table.
11. Pregnant or lactating females or females planning to become pregnant during the study period.
12. Other well documented causes of chronic liver disease according to standard diagnostic procedures including, but not restricted to:
    - Positive hepatitis B surface antigen (HBsAg)
    - Positive HCV RNA, (tested for in case of known cured HCV infection, or positive HCV Ab at Screening)
    - Suspicion of drug-induced liver disease
    - Alcoholic liver disease
    - Autoimmune hepatitis
    - Wilson's disease
    - Primary biliary cirrhosis, primary sclerosing cholangitis
    - Genetic homozygous hemochromatosis
    - Known or suspected HCC
    - History or planned liver transplant, or current MELD score >12.
13. Where applicable, patients not covered by Health Insurance System and/or not in compliance with the recommendations of National Law in force applicable to clinical trials.
14. Patients who cannot be contacted in case of emergency.
15. Known hypersensitivity to the investigation product or any of its formulation excipients.
16. Patients with previous exposure to elafibranor.
17. Patients who are currently participating in, plan to participate in, or have participated in an investigational drug trial or medical device trial containing active substance within 30 days or five half-lives, whichever is longer, prior to Screening.

Concomitant medications (see APPENDIX III: Permitted/non-permitted medication):

18. Fibrates are not permitted from 2 months before Randomization. Patients that used statins, ezetimibe, or nonfibrate lipid lowering drugs before Screening may participate if the dosage has been kept constant for at least 2 months prior to Screening.
19. Currently taking drugs that can induce steatosis/steatohepatitis including, but not restricted to: corticosteroids (parenteral & oral chronic administration only), amiodarone (Cordarone), tamoxifen

(Nolvadex), and methotrexate (Rheumatrex, Trexall), which are not permitted 30 days prior to Screening and up to end of treatment.

20. Currently taking any medication that could interfere with study medication absorption, distribution, metabolism, or excretion or could lead to induction or inhibition of microsomal enzymes, e.g., indomethacin, which are not permitted from Randomization until end of treatment.

Associated illnesses or conditions:

21. Any medical conditions that may diminish life expectancy to less than 2 years including known cancers.
22. Evidence of any other unstable or, untreated clinically significant immunological, endocrine, hematological, gastrointestinal, neurological, neoplastic, or psychiatric disease
23. Mental instability or incompetence, such that the validity of informed consent or ability to be compliant with the study is uncertain.

In addition to the above criteria, patient should not present any of the following biological exclusion criteria:

24. Positive anti-human immunodeficiency virus (HIV) antibody.
25. AST and/or ALT >10 x upper limit of normal (ULN).
26. Conjugated bilirubin >1.50 mg/dL due to altered hepatic function. Note: Gilbert Disease patients are allowed into the study.
27. INR >1.40 due to altered hepatic function.
28. Platelet count <100,000/mm3 due to portal hypertension.
29. Serum creatinine levels >1.53 mg/dL in males and >1.24 mg/dL in females.
30. Significant renal disease, including nephritic syndrome, chronic kidney disease (defined as patients with markers of kidney damage or eGFR of less than 60 ml/min/1.73 m2).
31. Unexplained serum CPK >3 x the ULN. In case of explained elevated CPK >3 x the ULN, the measurement can be repeated prior to Randomization. In this case, retest should be performed within 1 to 2 weeks after initial test. A CPK retest >3 x ULN leads to exclusion.

5. TRIAL PROCEDURES

The procedures performed at each visit are summarized in the study schedules (see Table 1, Table 2, Figure 1, and Figure 2) and in Section 3.

The Investigator will be asked, whenever possible, to schedule patient visits at the same time of day for each patient. A patient may be seen at any time for reasons of safety.

During each visit, lifestyle and study recommendations will be repeated, vital signs will be measured, and the patient will be queried in the form of an open question regarding new or continuing events.

Procedures for premature discontinuation after SV1 are described in Section 5.2.

5.1. LIFESTYLE RECOMMENDATIONS AND STUDY RECOMMENDATIONS

5.1.1. Standard diet and exercise recommendations

Standard diet and exercise recommendations given by the Investigator during SV1 will be given at the beginning of each patient's participation and will be maintained throughout the study. These recommendations will be based on Therapeutic Lifestyle Change (TLC) counseling (or local equivalent) according to NCEP ATP III guidelines. The essential components of TLC and the macronutrient recommendations for the TLC diet are detailed in APPENDIX II: Adequate diet and lifestyle recommendations.

Assessment of dietary and lifestyle compliance will occur at each visit by asking the patient 2 questions to confirm if they have remained compliant to the diet and lifestyle recommendations. A yes/no response will be recorded in the electronic care report form (eCRF).

5.1.2. Dietary, fluid, and lifestyle restrictions

The following restrictions should be applied to patients in this trial from SV1 through to the end of the study:

- Patients will be required to fast (no food or drink other than water) for at least 12 hours prior to all blood sampling. As such, patients should not consume any breakfast or take any medication (including study medication) in the morning prior the blood sampling. In case the patients do not fast before a visit, a new appointment will be scheduled within 7 days.
- On each study visit day, study treatment will be taken under fasting conditions after the blood sampling (which corresponds to the day of the visit).
- During the 48 hours preceding each study visit, patients should not perform strenuous exercise.
- Patients are to avoid consumption of dietary supplements such as anti-oxidant (including, but not limited to Vitamin A, Vitamin C, provitamin A, selenium, and polyphenol).
- Alcohol consumption should be limited during the study duration and registered in the eCRF. Alcohol consumption of more than 20 g per day for women and 30 g per day for men is considered abusive

(see APPENDIX IV: Alcohol comparison table). A standard drink is equal to 14.0 grams (0.6 ounces) of pure alcohol. Generally, this amount of pure alcohol is found in:

- 12-ounces/350 ml of beer (5% alcohol content)
- 5-ounces/150 ml of wine (12% alcohol content)
- 1.5-ounces/50 ml (40% alcohol content) distilled spirits or liquor (e.g., gin, rum, vodka, whiskey).

Concomitant therapy is restricted and any change to treatment or introduction of a new treatment should be discussed with the Investigator before doing so (see Section 7.12 and APPENDIX III: Permitted/non-permitted medication).

5.1.3. Home pregnancy test for women of childbearing potential

Women of childbearing potential are required to perform a pregnancy test every 4 weeks. Home pregnancy test kits will be supplied at each visit to WOCBP and these are to be performed as per the kit instructions every 4 weeks between study visits. Negative results are to be reported at the next scheduled visit or telephone visit (see Table 1 and Figure 2). In the event of a positive result the patient must discontinue study drug immediately and report the result to the Investigator as soon as possible (see Section 8.6.1).

5.1.4. Sun exposure

As a conservative approach patients will be advised to avoid extended ultra-violet light exposure without protection from V1 through to the end of the study (see Section 1.4.4.4).

5.2. PATIENT WITHDRAWAL AND PATIENT TREATMENT DISCONTINUATION RULES

5.2.1. Handling of patient withdrawal

Patients will be informed that they have the right to discontinue the study at any time, for any reason, without affecting future management and treatment.

5.2.2. Permanent discontinuations of study drug

In some instances, it may be necessary for a patient to permanently discontinue study drug. The patient may be discontinued from study drug at any time at the discretion of the Investigator or Sponsor for safety, behavioral, or administrative reasons. In keeping with the ITT analysis, the patient will not be permanently discontinued from the study.

The reason for permanent discontinuation of study drug should be documented in the eCRF and the Medical Monitor informed. If the discontinuation of study drug is due to an AE, the event should be documented in the eCRF.

Some possible reasons that may lead to permanent early study drug discontinuation include:

- Occurrence of any event listed in the composite endpoints for long-term efficacy evaluation (see Section 1.9.2)
- In the opinion of the Investigator, any AE, SAE (described in Section 8), or significant change in a laboratory value that warrants permanent discontinuation of study drug therapy. Investigators are advised to call the Medical Monitor prior to making such a decision
- Occurrence of repeated hypoglycemic episodes without possibility for a down titration of background therapy that may put the patient at risk with continued participation
- Non-permitted concomitant medication (described in Section 7.12 and APPENDIX III: Permitted/non-permitted medication)
- Female patients who are pregnant (see Section 8.6.1) or are breastfeeding or who do not agree to use a reliable method of birth control during the study will be permanently discontinued from study drug
- Non-compliance with the study treatment
- Uncooperative patient
- The patient requests to stop study drug permanently.

Patients permanently discontinued from study drug will be requested to stop taking study drug and attend an EOT Visit 30 days after the last administration of study drug (described in Section 3.9).

If the study drug is discontinued due to the occurrence of any event listed in the composite endpoints for long-term efficacy evaluation (see Section 1.9.2), the patient will also be discontinued from the study with no further follow-up after the EOT Visit.

If the study drug is discontinued due to any reason other than the occurrence of any event listed in the composite endpoints for long-term efficacy evaluation, the patient will undergo, if agreed, telephone visits every 24 weeks (described in Section 3.10) after the EOT Visit until the EOS or the occurrence of any event listed in the primary composite endpoints for long-term efficacy evaluation (see Section 1.9.2), whichever is sooner.

5.2.3. Patient discontinuation from the Study

Patient discontinuation prior to the patient's completion of the study is expected to be low, occurring if the patient withdraws consent, or if enrollment in any other clinical trial involving an investigational product, or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study, occurs.

At the time of discontinuing from the study, the Medical Monitor and IXRS should be contacted, and, if possible, an EOT Visit should be conducted (see Section 3.9). The patient will be permanently discontinued from the study at that time with no further follow-up and the date the patient is withdrawn from the study and the reason for withdrawal should be appropriately documented in the eCRF. During the study close-out

period, survival status will be collected within legal and ethical boundaries for all patients randomized who withdrew participation from the study.

Where possible, patients withdrawn from the study will be followed until resolution of all their SAEs or until the unresolved SAEs are judged by the Investigator to have stabilized.

5.2.4. Patients lost to follow-Up

A patient would be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. Site personnel are expected to make diligent attempts to contact patients who fail to return for a scheduled visit or were otherwise unable to be followed up by the site. Vital status will be collected within legal and ethical boundaries for all patients randomized, including those who did not get study drug. Vital status will be searched in public sources during the study close-out period. If vital status is determined, the patient will not be considered lost to follow-up.

5.2.5. Replacement

No patient replacements are permitted in this study.

5.2.6. Premature discontinuation of the study

Premature termination of this clinical trial may occur because of a Regulatory Authority decision, change in opinion of the IRB/IEC, drug safety problems, DSMB recommendations, or at the discretion of the Sponsor. In addition, the Sponsor retains the right to discontinue development of the study treatment at any time.

The Sponsor reserves the right to discontinue the trial prior to inclusion of the intended number of patients, but intends only to exercise this right for valid scientific or administrative reasons. After such a decision, the Investigator must contact all participating patients within a reasonable period of time. As directed by the Sponsor, all trial materials must be collected and all eCRFs completed to the greatest extent possible.

Furthermore, the Investigator can decide to prematurely discontinue the study. In that event, the Investigator must notify the Sponsor immediately of his/her decision and give the reason in writing. Prompt compliance with this requirement is essential so that the Sponsor may comply with its regulatory obligations.

In all cases, ethics committee (IRB/IEC) and Health Authorities should be informed.

If the Investigator decides to prematurely discontinue the study, all test articles, eCRFs, and related study materials must be returned to the Sponsor.

5.3. PATIENT RESCREENING

Re-screening is allowed in a screen failed patient if there is a change in the situation of the patient which allows him/her to fulfill inclusion/exclusion criteria. This will need sponsor approval. In case of re-screening

the patient will need to sign a new informed consent and will be entered as a new patient, with a new patient number.

6. ASSESSMENTS

6.1. EFFICACY AND SAFETY ASSESSMENTS

6.1.1. Histological assessments

A liver biopsy (see Section 6.1.1.1 for recommendations) will be performed:

- At baseline
- After 72 weeks of treatment
- After approximately 4 years of treatment (V13) unless a biopsy has been performed within the previous year.
- In the case cirrhosis is suspected at any interim visit during the LTPP (based on FibroScan and/or clinical and biological assessments)

A Laboratory Manual will be provided to each trial site. The manual will outline the collection process, and shipping requirements for the specific central laboratory.

6.1.1.1. Recommendations related to liver biopsy

Before performing a percutaneous liver biopsy, there must be a clearly defined indication for the biopsy, and the risks to the patient should not outweigh the potential benefits. This will be assessed by the investigator according to local practice.

The patient's platelet count and PT should be checked according to local hospital standards before the date of liver biopsy. Local guidelines and thresholds for hemostatic parameters should be used as they are in everyday clinical practice. Usually a platelet count >80,000/mm^3, a PT >60% or longer by no more than 4 seconds over the control, and a normal bleeding time are acceptable for performing percutaneous liver biopsy in a patient that has stopped taking any antiaggregant therapy for >5 days. If these conditions are not all respected, a safer option would be to perform the liver biopsy by transjugular route, when available.

Sedation is recommended to be given for percutaneous liver biopsy, and should be given with caution in liver disease.

The recommended biopsy procedure to be applied is:

- Needle core biopsy
- Biopsy obtained with a 16 or lower gauge needle
- A tissue core ≥2 cm long (≥10 portal tracts) represents optimal biopsy length
- Preferably obtain biopsy from the right lobe. If left lobe biopsy is used for inclusion, a left lobe biopsy should be used for future biopsies.

Post-biopsy observation: It is recommended that the patient should remain in hospital at least for 6 hours after the procedure.

The biopsies will be sent to the central laboratory and then to a central reader who will read the biopsies to determine the eligibility to the study according the fibrosis stage and consistency with NASH diagnosis. Biopsy slides will be blinded for patient and visit identification prior to central reading.

In case the liver biopsy fragment is too small or of bad quality, thereby precluding adequate reading, other available slides or new slides to be prepared from an available block of tissue may be requested to the site.

6.1.1.2. Liver biopsy reading for NAS and NASH CRN fibrosis score

Histological changes from baseline to Week 72 and any follow-up biopsy will be evaluated. Liver biopsy samples will be sent to the central pathology laboratory (Liverpat, 28 rue de l'amiral Hamelin, 75 116 Paris–France) where they will be read and scored. Scores for total NAS, steatosis, ballooning, lobular inflammation, or portal inflammation, as well as fibrosis scores (both by NASH CRN scoring system, and NAFLD Ishak scoring system) and fibrosis area by morphometry will be evaluated.

6.1.2. Biological assessments

All blood samples for efficacy and/or for safety assessment (as described in Table 2) will be returned and centralized by the central laboratory (BARC: Ghent – Belgium, New York – USA, Sydney – Australia, or Johannesburg – South Africa) and specific analyses will be performed by another laboratory (GENFIT- Loos, France).

A laboratory manual will be provided to each trial site.

The manual will outline the collection process and shipping requirements for the specific central laboratory. Blood sampling will be performed by trained personnel at each site. Blood samples will be processed and shipped as outlined in the laboratory manual. Refer to the laboratory manual for exact amounts of blood required for each test.

For all visits, reportable laboratory results (except serology) will be available at sites approximately 24 hours after receipt of samples. Final results will be sent to sites. Laboratory reports should be reviewed, signed, and dated by the Investigator as soon as they are received. The Investigator should comment upon out of range parameters and assess clinical significance.

The option to retest during the study is left to the Investigator's judgment. During Screening, retesting (to be performed at retesting screening visits) is limited to HbA1c, CPK, and HCV RNA, as described Section 3.11. Any other retest deemed necessary by the Investigator should be discussed with the Study Medical Monitors.

In case the lab sampling may not be performed at the scheduled visit, patients should come back to the site within 7 days of the visit for lab sampling.

6.1.2.1. Laboratory assessments

Clinical laboratory evaluations (including hematology, blood chemistry, and urinalysis) will be measured at every visit as described in Table 2.

Hematology and urinalysis (dipstick) will be measured at all visits. Both blood and urine sample will be transported to the central laboratory for testing and analysis. At Screening, the Screening Visit 1 chemistry panel will be measured.

The V1 to Vn total chemistry panel and urine analysis will be measured at all visits from V1 to EOT visits. It is recommended to collect first morning urine samples for urinalysis.

6.1.2.2. Urinary pregnancy tests

Urinary pregnancy tests will be supplied to each site to perform a pregnancy diagnostic at each visit during the study on WOCBP. These tests will also be given to the WOCBP to perform a pregnancy test at home every 4 weeks in between visits (see Section 5.1.3).

6.1.2.3. Serology (SB1)

Screens for a hepatitis panel and HIV antibodies will be performed at SV1:

- HIV ab I/II
- HBsAg
- HCV ab (in case of known cured HCV infection, HCV RNA can be tested directly at SV1; otherwise, HCV RNA should be tested at a Retesting Screening Visit, only in case HCV ab>0 at SV1 [see Section 3.11.1])

6.1.2.4. Other parameters

Liver markers, calculated fibrosis and steatosis index, safety, and inflammatory markers, as well as special glycemic and lipid parameters, will be measured at V1, V3, V5, and V7 during the First Treatment Period, at each visit during LTTP, and at the EOT visit. CHI3L1 will only be tested at V1, V7, and V13 (at the time of the approximate 4 year biopsy).

6.1.3. Constitution of biobank

In order to be able to test other specific parameters which could be of interest regarding the elafibranor development program or regarding diagnosis, prevention, or treatment of NASH or other related diseases, an additional amount of serum & plasma will be kept at each visit (including screening visits) from patients who have given their consent for these additional analyses by signature of the genetic and biomarker ICF.

These samples will be used:

- To discover or validate biomarkers in NASH and related diseases.
- To investigate the role of selected single nucleotide polymorphisms in the response to treatment.

These samples will be destroyed 3 years after study results at the latest.

6.2. OTHER SAFETY ASSESSMENTS AND ONGOING SAFETY MONITORING

6.2.1. Physical examination

A physical examination will be performed and weight measured at each visit (with the exception of the potential SV2). Height will be measured at SV1 only.

The patient's weight will be measured under the same conditions at each visit. Where possible, the scale for weight must be the same for a given patient throughout the visits.

6.2.2. Waist circumference

Waist circumference will be measured at the midpoint between the lateral iliac crest and the lowest rib in cm during expiration. The measuring tape should be snug but not compressing the skin and held parallel to the floor. The measurement is to be made at normal respiration.

6.2.3. Vital signs

Blood pressure (mmHg) and pulse rate (beats per minute) will be measured at each visit (with the exception of the potential SV2 visit) according to the "Recommendations for Blood Pressure Measurement in Humans and Experimental Animals" published in an American Heart Association scientific statement.

6.2.3.1. Important points for clinical blood pressure measurement

- The patient should be seated comfortably with the back supported and the upper arm bare without constrictive clothing. The legs should not be crossed.
- The arm should be supported at heart level, and the bladder of the cuff should encircle at least 80% of the arm circumference.
- When using a mercury sphygmomanometer, the mercury should be deflated at 2 to 3 mm/s, and the first and last audible sounds should be taken as systolic and diastolic pressure. The column should be read to the nearest 2 mmHg.
- Neither the patient nor the observer should talk during the measurement.

Systolic BP and diastolic BP will be measured after 5 minutes rest in the seating position with a standard mercury sphygmomanometer or a validated sphygmomanometer. Where possible, the validated manometer should be the same for a given patient throughout the visits.

6.2.4. Electrocardiogram

A standard 12-lead ECG will be obtained at V1, V4, and V7 in the First Treatment Period, every 48 weeks in the LTTP starting at V9, and at the EOT visit.

Electrocardiograms will be recorded using 12-lead ECG recorders following 10 minutes rest in the supine position. A minimum of 3 cycles will be recorded per lead.

The ECGs will be analyzed by the Investigator. Any potential clinical significance of ECG changes will be determined by the Investigator with relation to the patient's medical history, physical examination, and concomitant medications and recorded in the eCRF.

6.2.5. FibroScan

A FibroScan exam will be performed at V1 and V7 in the First Treatment Period and at each visit in the LTTP. Where possible, FibroScan must be done at the day of visit. Otherwise, it can be performed within 7 days around the visit date.

Recommendations for ensuring a reliable examination are:

- Patient must be fasting for at least 2 hours before the FibroScan examination
- At least 10 consecutive and successful measurements shall be performed without changing probe position
- InterQuartile Range (IQR)/Median stiffness ratio (in %) shall remain <30% at the end of the scan, to consider a FibroScan measure as reliable. If not, it is recommended to perform a few additional individual measures, or to restart the entire FibroScan examination

6.2.6. Quality of life questionnaire

A standardized and validated questionnaire for quality of life (SF-36) will be completed by patients at V1, V3, V5, and V7 in the First Treatment Period, and V8, V9, V11, and every 48 weeks thereafter in the LTTP until, and including the EOT visit.

6.3. IMPORTANT SPECIFIC BIOLOGICAL CONSIDERATIONS AND PATIENT DISCONTINUATION RULES

6.3.1. Creatine phosphokinase

If at any visit during the treatment periods, a patient experiences diffuse myalgia, muscle tenderness, and/or marked increase in muscle CPK values (≥3 x ULN and ≤5 x ULN), an additional visit and test within 3 to 7 days must be performed. If, during that visit, the patient still experiences diffuse myalgia, muscle tenderness and/or marked increase in muscle CPK values (≥3 x ULN and ≤5 x ULN), myopathy must be considered and

the patient must be discontinued from study treatment immediately and followed up as described in Section 5.2.2.

If at any visit during the treatment periods, a patient experiences marked increase in muscle CPK values >5 x ULN, unexplained by strenuous exercise or trauma, the patient must be discontinued from study treatment immediately and followed up as described in Section 5.2.2. In case of exercise and/or trauma, the CPK should be repeated once weekly to verify decrease of CPK, until CPK lowers to ≤5 x ULN.

6.3.2. Liver function monitoring

All liver decompensation events included in the composite efficacy endpoint (Section 1.9.2) will be adjudicated by the Clinical Events Committee (CEC; see Section 6.5), as well as all DILI events (see Section 6.5).

For DILI adjudication, assessment may be performed using as baseline either historical AST, ALT, total bilirubin, and INR results meeting the requirements of within 8 weeks to 6 months of planned randomization visit (V1), or, using lab results from SV1 and V1 that are at least 8 weeks apart.

In all cases, whether baseline AT values are normal or elevated, an increase of AT >10 x ULN will lead to permanent discontinuation of the patient from study drug, and scheduling of EOT visit (Section 3.9).

6.3.2.1. Monitoring of patients with normal baseline aminotransferase values

Liver function monitoring requirements for patients with normal baseline AT values at V1 who at any visit from V2 onwards during the treatment periods exhibit:

- Increase in AT to ≤3 x ULN: no additional action required, schedule next visit as per assessment schedule
- Increase in AT to >3 x ULN but ≤5 x ULN: retest after 48 to 72 hours
  If during the following retest:
  - AT remains >3 x ULN but ≤5 x ULN: continue the drug with close serial monitoring (once a week)
  - AT increases to >5 x ULN: permanently discontinue patient from study drug and schedule EOT Visit (see Section 3.9 and Section 5.2.2).
- Increase in AT >5 x ULN: retest after 48 to 72 hours
  If during the following retest:
  - AT remains >5 x ULN: permanently discontinue patient from study drug and schedule EOT Visit (see Section 3.9 and Section 5.2.2)
  - AT reduces to ≤5 x ULN: continue the drug with close serial monitoring (once a week).
- Increase in AT >3 x ULN AND increase in total bilirubin >2 ULN: permanently discontinue patient from study drug and schedule EOT Visit (see Section 3.9 and Section 5.2.2).

- Increase in AT >3 x ULN AND increase in INR>1.5 (except in case of anticoagulant therapy): permanently discontinue patient from study drug and schedule EOT Visit (see Section 3.9 and Section 5.2.2).
- Increase in AT >3 x ULN AND fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash: permanently discontinue patient from study drug and schedule EOT Visit (see Section 3.9 and Section 5.2.2).
- Increase in AT >3 x ULN AND eosinophilia (>5%) with total count > ULN: permanently discontinue patient from study drug and schedule EOT Visit (see Section 3.9 and Section 5.2.2).

6.3.2.2. Monitoring of patients with increased baseline aminotransferase values

Liver function monitoring requirements for patients with increased AT baseline values at V1 who at any visit post V1 onwards during the treatment periods exhibit:

- Increase in AT to ≤3 x baseline value: no additional action required, schedule next visit as per assessment schedule
- Increase in AT to >3 x baseline value but ≤10 x ULN: retest after 48 to 72 hours
    - AT remains >3 x baseline value but ≤10 x ULN: continue the drug with close serial monitoring (once a week)
    - AT increases >5 x baseline value or >10 x ULN: permanently discontinue patient from study drug and schedule EOT Visit (see Section 3.9 and Section 5.2.2).
- Increase in AT >3 x baseline value AND increase in total bilirubin > 2 x ULN: permanently discontinue patient from study drug and schedule EOT Visit (see Section 3.9 and Section 5.2.2).
- Increase in AT >3 x baseline value AND increase in INR>1.5 (except in case of anticoagulant therapy): permanently discontinue patient from study drug and schedule EOT Visit (see Section 3.9 and Section 5.2.2).
- Increase in AT >3 x baseline value AND fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash: permanently discontinue patient from study drug and schedule EOT Visit (see Section 3.9 and Section 5.2.2).
- Increase in AT >3 x baseline value AND eosinophilia (>5%) with total count > ULN: permanently discontinue patient from study drug and schedule EOT Visit (see Section 3.9 and Section 5.2.2).

6.3.3. Threshold for diagnosis of cirrhosis

A FibroScan and serum markers assessments will be performed every 24 weeks at each visit in the LTTP.

A liver biopsy may be considered in order to confirm the diagnosis of cirrhosis if during a LTTP visit the FibroScan value is ≥ 14 kPa (with IQR/Median stiffness ratio < 30%*) associated with a platelet count <150 000/mm^3 and at least 1 elevated serum marker of fibrosis indicative of cirrhosis (calculated NAFLD fibrosis >0.676 score or reported FIB-4 >2.67).

**InterQuartile Range (IQR)/Median stiffness ratio (in %) shall remain <30% at the end of the scan, to consider a FibroScan measure as reliable. If not, it is recommended to perform a few additional individual measures, or to restart the entire FibroScan examination.*

In the case of detection of variceal rupture at endoscopy or of presence of any cirrhosis related event, such as MELD ≥15, hepatic encephalopathy, or ascites, then the liver biopsy will not be required for diagnosis of cirrhosis, but the diagnosed event will have to be adjudicated by the CEC.

If cirrhosis or any event listed in the long-term composite endpoint is diagnosed, the patient will discontinue the study drug and the study and will be followed up as described in Section 5.2.2 and Section 5.2.3.

6.4. SAFETY & EFFICACY DATA REVIEW

An independent DSMB will be established in order to review the progress of the study and to perform a safety data review on a regular basis during the trial to protect patient welfare and preserve study integrity. The DSMB will also review the interim analysis results and provide final recommendations regarding trial termination due to futility and adjustment of the target number of primary events. A detailed description of the interim analysis procedures and decision-making process will be provided in the DSMB Charter.

The DSMB will consist of at least 5 experienced physicians (1 endocrinologist, 1 cardiologist, 1 hepatologist, 1 oncologist, and 1 nephrologist) and 1 statistician, all of whom will be independent of the participants in the study. The DSMB Charter will define the role, responsibilities, rules, and tasks of the DSMB.

6.5. CLINICAL EVENT COMMITTEE

The CEC will conduct adjudication of all disease progression events included in the primary composite efficacy long-term endpoint (Section 1.9.2, except for histological cirrhosis), all DILI events, and all major cardiovascular events as defined in the CEC charter. The CEC assessment and adjudication will occur in a blinded, consistent, and unbiased manner throughout the course of a study to determine whether the endpoints meet the protocol-specified criteria.

The CEC will be comprised of 2 hepatologists, 2 cardiologists, and 1 endocrinologist, all of whom will be independent of the participants in the study.

6.6. GUIDANCE FOR INVESTIGATORS

6.6.1. Summary of safety data

The safety and tolerability of elafibranor were confirmed in Phase I and Phase II studies.

A Phase I program to assess the safety and tolerability, as well as the PK profile, of elafibranor has been conducted through 12 completed and 5 ongoing clinical trials. A total of 659 volunteers were randomized in these studies performed in Phase I centers, including 561 healthy lean subjects, 60 overweight or obese subjects, and 12 patients with type 2 diabetes, 6 with end stage renal disease and 20 with hepatic impairment

(Child-Pugh class A, B or C) have been randomized to date in the completed trials. Elafibranor daily doses ranged between 5 mg and 360 mg, with a treatment duration up to 16 days.

A Phase II program was initiated to assess the safety and efficacy profile of elafibranor in patients suffering from cardiometabolic disorders and NASH. To date, 5 Phase IIa studies have been completed in which 297 patients were randomized. A Phase IIb trial has been completed, and evaluated the efficacy and safety of elafibranor 80 mg and 120 mg on steatohepatitis in 274 patients with NASH. A Phase 2 study (GFT505B-216-1) was also conducted in Primary Biliary Cholangitis (PBC) and included 45 patients with PBC and inadequate response to UDCA. This study evaluated the efficacy and safety of elafibranor at doses of 80 mg and 120 mg after 12 weeks of treatment. In the Phase 2 program, the elafibranor daily doses ranged between 30 mg and 120 mg, with a maximum treatment duration of 12 months.

Of the 63 Treatment emergent SAEs that have been reported cumulatively in the completed clinical development program, 50 occurred with elafibranor and 13 with placebo. For all SAEs, the treatment code has been broken (end of study unblinding).

Of the 50 SAEs that occurred with elafibranor, only 10 SAEs reported in 7 subjects were considered as having a reasonable possibility of relationship to elafibranor by the investigators (serious adverse reaction). They consisted of:

- Atrial fibrillation in a patient with history of arterial hypertension and suspected chronic coronary disease treated with elafibranor 80 mg
- Acute cholecystitis and pancreatitis that occurred in a patient on the second day of drug administration of elafibranor 80 mg
- Spontaneous abortion in a pregnant patient treated for 6 months with elafibranor 80 mg
- Ataxia, tremor and fasciculations in a patient treated for 51 weeks with elafibranor 80 mg
- Acute pancreatitis that occurred after 7 weeks of treatment in a patient treated with elafibranor 120 mg.
- Parkinson's disease in a patient treated for 12 months with elafibranor 120 mg, aged 76 years (in the risk group for Parkinson's disease, and with a family history of Parkinson's disease).
- Autoimmune hepatitis in a 56-year-old subject after 12 weeks of treatment of 120 mg elafibranor. The subject received her last dose of investigational product before the event.

For atrial fibrillation, acute cholecystitis and pancreatitis, and Parkinson's disease, after later investigations, given the medical history of the patients or the time of occurrence of the event, relationship to elafibranor was judged as "no reasonable possibility" by the Sponsor.

All adverse reactions (adverse events reported by investigators as possibly related or related to study drug) reported in more than 1% of patients treated with elafibranor in clinical studies with repeated doses of at least 80 mg elafibranor per day are summarized in Table 3.

Table 3: Overview of the common nonserious adverse reactions (>1% of patients treated with elafibranor) by system organ class (SOC) reported in completed elafibranor clinical studies with repeated administration of elafibranor (at least 14 days) from 80 mg/day up to 300 mg/day (MTD)

System Organ Class	Adverse Reaction	Severity	Number of cases (Frequency %)
Gastrointestinal disorders	Diarrhea	Mild to moderate	17 (2.8%)
	Vomiting	Mild to moderate	9 (1.5%)
General disorders and administration site conditions	Fatigue / Asthenia	Mild to moderate	17 (2.8%)
Investigations	Hepatic enzymes increased (mainly transaminases)	Mild to severe	13 (2.1%)
	Blood creatine phosphokinase increased	Mild to moderate	6 (1.0%)
Musculoskeletal and connective tissue disorders	Myalgia	Mild to severe	9 (1.5%)
Metabolism and nutrition disorders	Decreased appetite	Mild to severe	9 (1.5%)
Nervous system disorders	Dizziness	Mild to moderate	6 (1.0%)
Skin and subcutaneous tissue disorders	Rash	Mild to moderate	8 (1.3%)
Renal and urinary disorders	Renal failure/impairment	Mild to moderate	7 (1.1%)

Among the non-serious adverse reactions, the most frequent were gastrointestinal disorders and general disorders. The first ones consisted mostly of diarrhea, and vomiting. For general disorders, the main symptoms were fatigue / asthenia. These are considered common and expected.

Other non-serious adverse reactions reported in more than 1% of patients concerned changes in biological parameters such as liver enzymes increase (mainly AT), CPK elevation, or increase of creatinine (reported by investigators as renal failure and/or impairment due to the calculation of creatinine clearance by MDRD based on creatinine). Myalgia, decrease of appetite dizziness and rash were also reported in more than 1% of patients but remain limited.

Regarding specific monitoring, although no signal for increase in CPK has been observed in the clinical trials, given the known effects of PPARα agonists on the increase of CPK enzyme, this parameter is monitored in clinical trials. For this reason, it is recommended that investigators review these lab results in the course of clinical trials.

Other known effects of PPARα agonists include the increase of creatinine, which was observed in our phase IIa and IIb trials, in a range of 5-10%. This increase was reversible at end of treatment. This should also be monitored in clinical trials.

Liver enzymes will also be monitored in clinical trials, with specific attention paid to DILI.

Based on the findings of nonclinical reproductive and developmental toxicity studies performed to date, and in the absence of human pregnancy data, elafibranor may be classed in the "Possible human teratogenicity/fetotoxicity in early pregnancy" risk category according to the Clinical Trial Facilitation Group (CTFG) document Recommendations related to contraception and pregnancy testing in clinical trials (September 2014)[34].

As such, all clinical trials with elafibranor including WOCBP request a negative pregnancy test before Randomization, with highly effective contraceptive measures throughout the study. It is recommended to maintain the contraception up to 1 month after end of treatment. Pregnancy tests should be repeated as stated in each study protocol.

6.6.2. Safety data conclusion

Based on the cumulative experience gathered to date, gastro-intestinal disorders and asthenia / fatigue are considered common non-serious adverse reactions reasonably associated with elafibranor. Most of them are of mild to moderate intensity. Laboratory increases in serum creatinine or CPK should be monitored throughout clinical trials as this has been observed in Phase II trials to date, and is a known PPARα agonist effect. Elevation of AT will be monitored as well as DILI. In the absence of extensive human pregnancy data, highly effective contraception should be maintained for women of childbearing potential participating in clinical trials with elafibranor treatment, up to 1 month after end of study treatment.

6.6.3. Benefit/risk assessment

Numerous Phase I and Phase IIa clinical studies have provided data that support the therapeutic potential of elafibranor in metabolic diseases including NASH. Moreover, the Phase IIb trial demonstrated the efficacy of elafibranor at the therapeutic dose of 120 mg on a clinically meaningful primary endpoint, resolution of histological NASH without worsening of fibrosis, in patients with active disease (NAS ≥4). While the trial was short and not designed for antifibrotic endpoints, it nonetheless showed that elafibranor, at 120 mg daily, improved fibrosis indirectly through the resolution of NASH. Importantly, elafibranor 120 mg concomitantly improved the cardiometabolic risk profile of the patients by decreasing plasma triglycerides, total and LDL-cholesterol, increasing HDL-cholesterol, and improving inflammation, insulin resistance, and glucose homeostasis. Together these results position elafibranor as a drug candidate to treat NASH with the objective to block fibrosis evolution and ultimately avoid long term liver outcomes while reducing cardiovascular risk.

Furthermore, the Phase IIa trial in PBC subjects who had an inadequate response to UDCA demonstrated similar improvement in GGT, lipid and inflammatory markers. Moreover, a significant decrease of ALP levels

was observed, resulting in significant treatment effects versus placebo on the primary endpoint, whilst also meeting the composite endpoint used for drug registration (i.e. serum ALP <1.67 x ULN, an ALP decrease >15% and total bilirubin <ULN).

Moreover, these studies have highlighted the good safety profile of elafibranor and no major safety concerns have been raised.

Despite this favorable benefit-risk profile, an independent DSMB is to be established in order to review the safety of the treatment during the trial in an unblinded manner, to protect patient welfare and preserve study integrity. The safety assessments will be performed on a regular basis, every 6 months after Randomization of the first patient. The DSMB will consist of 5 experienced physicians (1 endocrinologist, 1 cardiologist, 1 hepatologist, 1 oncologist, and 1 nephrologist) and 1 statistician, all independent of the participants in the study.

In addition, throughout the study, patients will benefit from close safety monitoring including assessment of many safety parameters and follow-up of the disease progression, mainly through noninvasive measures including FibroScan.

7. TREATMENTS

7.1. DESCRIPTION OF STUDY MEDICATIONS

Elafibranor (propanoic acid, 2-[2,6-dimethyl-4-[3-[4-(methylthio)phenyl]-3-oxo-1(E)-propenyl] phenoxy]-2-methylpropanoic acid) will be supplied as 120 mg white to off-white round coated tablets with no printed inscription. The tablet contains elafibranor and inactive ingredients [redacted]

Placebo to match elafibranor 120 mg will be provided as a white to off-white round coated tablet with no printed inscription.

For additional information see Investigator's Brochure.

7.2. PACKAGING AND LABELING

7.2.1. Packaging

Elafibranor/placebo:

The primary packaging is composed of opaque polyamide/aluminum/PVC complex and aluminum foil blisters. This has been shown to be a suitable primary packaging for tablets.

Blisters, containing 8 tablets each, will be packed in child proof wallets.

Each childproof wallet will contain 4 blisters. Three wallets will be packaged inside a carton.

7.2.2. Labeling

All labels for study drugs meet all applicable requirements of the US Food and Drug Administration (FDA) and the EU annex 13 of Good Manufacturing Practices: Manufacture of Investigational Medicinal Products (February 2010) and /or other local regulations, as applicable.

Distribution of study drug will be performed according to the Good Distribution Practices.

Product cartons will be labeled with the protocol number, Sponsor's name and address, description of contents, storage conditions, expiry date, dosage instructions, and any other applicable items required by national and regional guidelines/regulations. The label will contain the statements "For clinical trial use only" or other similar/appropriate statements as well as the following instructions "Please return empty packaging and unused products to your doctor at your next visit." Details of carton and wallet labels are detailed in APPENDIX V: Product carton and wallet labeling.

7.3. DOSAGE AND ADMINISTRATION OF ELAFIBRANOR AND PLACEBO

Patients will be informed to take one tablet per day of elafibranor 120 mg or placebo orally before breakfast with a glass of water each morning.

7.4. METHOD OF ASSIGNING PATIENT TO TREATMENT GROUP

Upon screening of the first patient, the IXRS system will immediately forward the information to the Drug Distribution Center which will be responsible to send one of several blocks of treatment packages (containing 96 tablets to last approximately 3 months) allocated to the site. The pharmacy will acknowledge receipt of the study drug in the IXRS.

An e-mail, confirming that the patient has been screened, will be sent to the Investigator, [redacted] and to the Sponsor.

After having received the liver biopsy results as well as the SV1 laboratory results (SB1) (or when applicable, results of any retesting performed), and if the patient fulfills all criteria to enter the treatment period, the Investigator will register the patient in the IXRS to randomize him/her.

The IXRS will check if the Investigator is authorized to use the system (identification number and access code) and will ask some questions to check the patient eligibility. The IXRS will then allocate the patient to a treatment group (elafibranor 120 mg or placebo) through a patient number (with 9 digits), as described in Section 3.2.

A specific IXRS procedure manual will be provided to the pharmacy.

The randomization list will be generated by the IXRS partner and will be kept in blinding condition to the study participants until the final database lock and the Sponsor authorization to unblind the trial.

7.5. STORAGE CONDITIONS

Elafibranor and placebo should be stored between +15°C and +25°C (59°F and 77°F). Storage conditions are specified on the label.

7.6. DISPENSING OF TREATMENT

Each site will have a resupply strategy within the IXRS to determine the supply of study drugs sent to each site. Initial site shipments will be shipped at a static value defined in the supply strategy. Following randomization of a patient IXRS will project for the amount of study drug required for future visits and ensure the study drug is at site for the visits occurring. The IXRS will continue to project study drug requirements per patient until an event occurs which stops the projections for that patient.

The Investigator will register the patient's visit in the IXRS who will allocate to the patient a treatment package for approximately 3 months (96 tablets) in the First Treatment Period and for approximately 6 months (192 tablets) in the LTTP. An e-mail, confirming the registration, will be sent to the Investigator and to the Sponsor.

The treatment package will include a carton with 3 wallets of 4 blisters for the First Treatment Period and 2 cartons with 3 wallets of 4 blisters in the LTTP.

Each randomized patient will be given, from V1 and at every following visit, the study medication containing the adequate number of wallets to cover the drug administration for the period between visits. The time between visits will be 12 weeks ± 1 week (to a maximum of 96 days) during the First Treatment Period and 24 weeks ± 2 weeks (to a maximum of 192 days) between visits in the LTTP, which correspond to the number of tablets provided to the patient at each visit.

7.7. TREATMENT REPLACEMENT

A specific IXRS procedure manual will be provided to the Investigator and will detail the procedure in case of need of treatment replacement.

7.8. PROCEDURE FOR BLINDING

The Investigator, patient, and study personnel will be blinded to the treatment.

Identification numbers will be assigned to a patient at the Screening Visit. The number will also be reported in the eCRF. Upon completion of the Screening Visit(s), eligible patients will be randomly assigned to active treatment (elafibranor 120 mg) or placebo at the first visit of the First Treatment Period (V1).

7.9. PROCEDURE FOR UNBLINDING

The randomization code may be broken by the Investigator when urgent action is required for the clinical management of the patient. For each patient, the list of treatment numbers allocated to the patient will be stored in the IXRS. The Investigator will be able to unblind any treatment carton that was dispensed to the patient by connecting to the IXRS (**24-hour & 7-day access**) and entering their identification number and access code. A back-up phone Interactive Response Technology (IRT) module will also be available should the site be unable to access the internet. The IXRS will verify the authorization to unblind the entered treatment carton and the screen will then display the treatment group, when completed, a blinded confirmatory e-mail will be sent to the Investigator and the Sponsor.

The reason for unblinding should be clearly and fully documented by the Investigator.

7.10. STUDY DRUG COMPLIANCE

From V2 and at every following visit while the patient is being treated with study drug, the patient will be directed to bring back all used and unused cartons and blisters. Compliance will be checked by the Investigator during those visits and registered in the eCRF.

If treatment is interrupted, whatever the cause, duration and reason of the interruption should be documented.

7.11. TREATMENT ACCOUNTABILITY, RETRIEVAL AND DESTRUCTION.

The Investigator or pharmacist will acknowledge receipt for each study treatment on the day of receipt. A drug accountability record should be maintained by the person responsible for dispensing the trial medication to the patient.

All partially used or unused treatments will be inventoried by the monitor during and at the conclusion of the study.

On Sponsor request, the Drug Distribution Center will organize the retrieval of all treatments (used or unused) and will proceed to their destruction only after the Sponsor provides written authorization.

If the site has an appropriate Standard Operating Procedure (SOP) for drug destruction, the site may destroy used and unused study drugs in accordance with the site SOP and always after the drug accountability has been performed by the monitor.

If drug is destroyed in the site, the Investigator must maintain accurate records for treatment cartons destroyed recording:

- Treatment carton (kit) number (see APPENDIX V: Product carton and wallet labeling)
- Quantity destroyed
- Method of destruction
- Person who disposed the drug.

7.12. OTHER MEDICATION

7.12.1. Handling of concomitant medication

In a general manner, patients should be discouraged from starting any new medication without consulting the Investigator unless the new medication is required for emergency purpose. In the same way, any qualitative or quantitative change in concomitant therapy should be avoided, when possible (see table II, APPENDIX III: Permitted/non-permitted medication). In the event that it becomes necessary during the study, this should be recorded by the Investigator in the eCRF (including concomitant medications taken

within 6 months prior to Screening) and information should be communicated to the Medical Monitor in order to evaluate the risk of DDIs. This includes drugs used on a chronic as well as on an "as needed" basis.

7.12.2. Non-permitted medication (see Table I, APPENDIX III: Permitted/non-permitted medication)

The following medications are not allowed within the timeframe given in APPENDIX III: Permitted/non-permitted medication):

- Thiazoledinediones (glitazones [pioglitazone & rosiglitazone])
- Fibrates
- Corticosteroids (parenteral & oral chronic administration only)
- Amiodarone
- Tamoxifen
- Methotrexate
- Indomethacin.

The following medications are not allowed to be initiated prior to diagnostic liver biopsy and up to 72 weeks of treatment (see APPENDIX III: Permitted/non-permitted medication):

- GLP-1 agonist
- SGLT2 inhibitors.

If it is identified that these non-permitted drugs have been administered to a patient within the excluded timeframes, the site will discuss the continuation of the patient with the Medical Monitors of the study.

7.12.3. Permitted medication under condition (see Table II, APPENDIX III: Permitted/non-permitted medication)

The following medications are permitted under the condition of steady dosage prior to Screening (dose changes are allowed after Randomization if judged necessary by the physician):

- Statins, ezetimibe, and other nonfibrate lipid lowering medications, provided the dosage is kept stable for at least 2 months prior to Screening.

The following medications are permitted under the condition of stable dose from at least 6 months prior to diagnostic liver biopsy (dose changes should be avoided up to EOT):

- Vitamin E >400 IU/day
- PUFAs >2 g/day
- UDCA.

The following medications are permitted under the condition of no qualitative change (i.e., implementation of a new antidiabetic drug) in the 6 months prior to diagnostic liver biopsy and up to Randomization:

- Insulin
- Sulfonylureas
- Metformin
- Gliptins
- SGLT2-inhibitors
- GLP-1 agonists.

Dose changes are allowed for these medications, except for GLP-1 agonists, which must be on stable dose in the 6 months prior to diagnostic liver biopsy and up to randomization.

In addition, no initiation of SGLT2-inhibitors and GLP-1 agonists is allowed from at least 6 months prior to the diagnostic liver biopsy up to 72 week of treatment (V7).

Patients on sulfonylureas and insulin are recommended to self-monitor blood glucose.

7.12.4. Permitted medication

Any medications other than those listed above are permitted. However, the dosage of a current medication for a chronic disease should remain unchanged as far as possible in order to reduce the risk of unknown DDIs.

In the event that additional concomitant therapy becomes necessary during the study, this should be recorded by the Investigator in the eCRF. This includes drugs used on a chronic as well as on an "as-needed" basis. Patients should be discouraged from starting any new medication without consulting the Investigator unless the new medication is required for emergency purpose.

8. ADVERSE EVENT AND TOXICITY MANAGEMENT

8.1. DEFINITIONS

8.1.1. Adverse events

Any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical (investigational) product and which does not necessarily have to have a causal relationship with this treatment will be considered as an AE. The term AE is synonymous with the term "adverse experience" as used by the FDA.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding or physiological observation, for example), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal product.

Examples of AE include (but are not limited to): abnormal test findings; clinically significant symptoms and signs; changes in physical examination findings; hypersensitivity; progression/worsening of pre-existing condition or underlying disease; recurrence of a pre-existing condition; lack of effect, complication, and termination of pregnancy.

Additionally, they may include the signs or symptoms resulting from: drug overdose, drug withdrawal, drug abuse, drug misuse, drug interactions, drug dependency, extravasation, exposure in utero.

The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

- Test result is associated with accompanying symptoms
- Test result requires additional diagnostic testing or medical/surgical intervention
- Test result leads to a change in trial dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy
- Test result is considered to be an AE by the Investigator or Sponsor.

Repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

An AE does not include the following:

- Medical or surgical procedures performed; the condition that leads to the procedure may be an AE if applicable
- Pre-existing disease, condition or laboratory abnormalities present or detected before the Screening Visit that do not worsen
- Overdose without clinical sequelae

- Any medical condition, or clinically significant laboratory abnormality with an onset before the consent form is signed. Such as medical condition is considered to be pre-existing and should be documented on the medical history of the eCRF
- Uncomplicated pregnancy
- An induced elective abortion to terminate a pregnancy without medical reason
- Events that are identified as efficacy endpoints for the long-term evaluation (described in Section 1.9.2) should not be reported as AE.

The questions concerning whether the condition existed before the start of the active phase of the study and whether it has increased in severity and/or frequency will be used to determine whether an event is a treatment-emergent AE. An AE is considered to be treatment emergent if (1) it is not present when the active phase of the study begins and is not a chronic condition that is part of the patient's medical history, or (2) it is present at the start of the active phase of the study or as part of the patient's medical history, but the severity or frequency increases during the active phase. The active phase of the study begins at the time of the first dose of the study drug. The active phase of the study ends at the last study visit.

8.1.2. Serious adverse events

A SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (see Section 8.1.2.1)
- Requires inpatient hospitalization or prolongation of existing hospitalization (see Section 8.1.2.2)
- Results in persistent or significant disability/incapacity (see Section 8.1.2.3)
- Is a congenital anomaly/birth defect (including fetal malformations associated with spontaneous abortions or elective abortions)
- Is another medically important condition (see Section 8.1.2.4).

In addition, any illnesses reported before starting active treatment or AE meeting the criteria of seriousness (as defined above) and considered to be possibly related (according to the Investigator) to any study-specific procedure (e.g., laboratory testing procedure, liver biopsy) must be reported as an SAE.

8.1.2.1. Life-threatening adverse events

- A life-threatening AE in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

8.1.2.2. *Inpatient or prolonged hospitalization*

An inpatient hospitalization or prolongation of a hospitalization means that the patient stays overnight in the hospital. An overnight stay is defined by hospitalization of 24 hours. Visits to the emergency room will not

be considered hospital admission. Pre-planned hospital stays or hospital stays for nonmedical social reasons will not be considered as hospitalization, for example:

- Hospitalization or prolongation of hospitalization is needed for a procedure required by the protocol. Day or night survey visits for biopsy or surgery required by the protocol are not considered serious.
- Hospitalization or prolongation of hospitalization is part of a routine procedure followed by the study center (e.g., stent removal after surgery). This should be recorded in the study file.
- Hospitalization for survey visits or annual physicals fall in the same category.
- Hospitalization planned before the start of the study for a pre-existing condition that has not worsened does not constitute an SAE (e.g., elective hospitalization for a total knee replacement due to a pre-existing condition of osteoarthritis of the knee that has not worsened during the study).

8.1.2.3. Significant or incapacitating disability

Only a persistent or significant or incapacitating disability is intended. This item refers to a substantial disruption of a person's ability to conduct normal life functions. Thus, disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma.

8.1.2.4. Medically important conditions

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

Examples of such events are:

- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias or convulsions that do not result in hospitalization
- Development of drug dependency or drug abuse.

8.1.3. Clarification on serious adverse events:

- Events that are identified as primary efficacy endpoints for the long-term evaluation should not be included as an AE.
- Death is an outcome of an AE, not an AE in itself.
- An SAE may occur even if the patient was not being treated with the investigational medicinal product at the occurrence of the event.
- Life-threatening means that patient is at immediate risk of death. This does not include an event that might have led to death if it had occurred with greater severity.

- Complications that occur during hospitalizations are AEs. If a complication prolongs the hospitalization, it is a SAE.
- Patient hospitalization means that the patient stays overnight in the hospital. Pre-planned hospital stays or hospital stays for nonmedical social reasons will not be considered as hospitalization.
- A procedure for protocol/disease-related investigations (e.g., biopsy) should not be reported as SAE. Hospitalization or prolonged hospitalization for a complication of such procedures should be reported as SAE.

8.1.4. Adverse drug reaction

An adverse drug reaction (ADR) is defined as a response to a medicinal product which is noxious and unintended and that is considered casually related to an investigational medicinal product. A serious ADR (SADR) is an ADR which meets the seriousness criteria.

8.1.5. Unexpected adverse event

Expectedness is assessed by the Sponsor. An unexpected AE is defined as an event that has a nature of severity or specificity that is not consistent with the applicable Investigator Brochure or that is symptomatically and pathophysiologically related to a known toxicity but differs because of a greater severity or specificity.

"Unexpected" refers to an ADR that has not been previously observed and reported rather than an event that has not been anticipated based on the properties of the drug.

8.2. ASSESSMENTS

The Investigator will establish whether or not any AE have occurred at each visit from the date of consent. The patient will be questioned in a general manner to determine specific symptoms without offering the patient any suggestion.

8.2.1. Intensity assessment

The intensity of the AE will be graded as follows:

- **Mild**: Awareness of signs or symptoms, but easily tolerated and are of minor irritant type causing no loss of time from normal activities. Symptoms do not require therapy or a medical evaluation; signs and symptoms are transient.
- **Moderate**: Events introduce a low level of inconvenience or concern to the participant and may interfere with daily activities, but are usually improved by simple therapeutic measures; moderate experiences may cause some interference with functioning.
- **Severe**: Events interrupt the participant's normal daily activities and generally require systemic drug therapy or other treatment; they are usually incapacitating.

8.2.2. Relation to the study treatment

The Investigator will make a clinical and scientific judgment regarding whether or not the AE was related to study treatment. The Investigator will evaluate any changes in laboratory values, make a determination as to whether or not the change is clinically important, and whether or not the changes were related to study drug. However, even if the Investigator feels there is no relationship to the study drug, the AE or clinically significant laboratory abnormality must be recorded in the eCRF.

The Investigator will record the relation to the study treatment according to the following causality terms:

- **Related:** the AE follows a reasonable temporal sequence from the time of drug administration and it cannot be explained by the patient's clinical state or the study procedures/conditions. The AE abates upon discontinuation of the study drug and reappears when the study drug is introduced.
- **Possibly related:** the AE follows a reasonable temporal sequence from the time of drug administration, but could have been produced by the patient's clinical state or the study procedures/conditions.
- **Unlikely related:** the temporal association between the AE and the study drug is such that the study drug is not likely to have any reasonable association with the AE. The relationship is not likely because of other plausible explanations.
- **Not related:** the AE must definitely be caused by the patient's clinical state or the study procedure/conditions. A reasonable explanation must be given, e.g., no investigational product taken, preplanned elective medical intervention, or incompatible temporal relationship.
- **Not assessable**: the report suggesting an adverse reaction cannot be judged because information is insufficient or contradictory and data cannot be supplemented or verified.

8.2.3. Action taken and outcome

The Investigator will record the action taken with drug and outcome of the event for each AE according to the following:

<u>Action taken with investigational drug</u>

- Drug permanently withdrawn – in case a patient is permanently withdrawn from the study drug
- Drug temporarily withdrawn – in case the study drug is temporarily withdrawn
- Dose not changed – in case no action is taken regarding the study drug
- Unknown
- Not applicable – an AE started before initiation of treatment with study drug, the treatment had been completed prior to reaction/event, or the patient has died.

<u>Outcome</u>

- Recovered/resolved

- Recovering/resolving
- Not recovered/not resolved
- Recovered/resolved with sequelae
- Fatal
- Unknown.

Note: In case of irreversible congenital anomalies the choice not recovered/not resolved should be used. "Fatal" should be used when death is possibly related to the reaction/event.

8.3. REPORTING

8.3.1. Reporting an adverse event

All AEs regardless of seriousness or relationship to study drug, including those occurring during the Screening Period, are to be recorded on the corresponding page(s) of the eCRF and in the patient's medical record from the ICF signature until study end for each patient. Whenever possible, symptoms should be grouped as a single syndrome or diagnosis. The Investigator should specify the date of onset, maximal intensity, action taken with respect to study drug, corrective therapy given, outcome, and his/her opinion as to whether there is a reasonable possibility that the AE was caused by the study drug.

Adverse event reporting begins from signature of the patient ICF at the first Screening Visit and ends at study end for each patient.

8.3.2. Reporting a serious adverse event

Serious AE reporting begins from signature of the patient ICF and ends at study end for each patient.

Any SAE that is brought to the attention of the Investigator at any time after the reporting period and which is considered by him/her to be caused by the study drug within a reasonable possibility, should be reported.

Any of the portal hypertension/cirrhosis related events described in Section 2.1.1 that are identified as potential primary efficacy endpoints for long-term evaluation will NOT be reported as SAEs unless it is determined by the adjudication committee that the event does not meet the predefined criteria for an endpoint. Events that are identified as potential primary efficacy endpoints for long-term evaluation that are not confirmed by adjudication will be reported as described with the start of the reporting time window being the time of negative adjudication decision.

Investigators must notify, by fax or e-mail, the Sponsor designated representative [redacted] of all SAEs **IMMEDIATELY (within 24 hours of the Investigator becoming aware of the event).**

ANY SERIOUS ADVERSE EVENTS, WHETHER OR NOT RELATED TO THE STUDY DRUG, MUST BE REPORTED IMMEDIATELY (WITHIN 24 HOURS) TO [redacted] AT THE FOLLOWING FAX NUMBERS:

FAX numbers: [redacted]

Contact Person: [redacted]

E-mail: [redacted]

All SAEs independent of the circumstances or suspected cause must be reported in ENGLISH on a SAE Form. The SAE Form should include a clearly written narrative describing signs, symptoms, and treatment of the event, diagnostic procedures, as well as any relevant laboratory data and any sequelae, in order to allow a complete medical assessment of the case and independent determination of the possible causality.

The Investigator is also required to submit follow-up SAE reports to [redacted] within 24 hours of becoming aware of additional information such as diagnosis, outcome, causality assessment, results of specific investigations, and any new significant information that has not been previously reported.

It is critical that the information provided on the initial or follow-up SAE Form matches the information recorded in the source documents and the eCRF for the same event.

Copies of additional laboratory tests, consultation reports, postmortem reports, hospital case reports, autopsy reports, and other documents should be sent when requested and applicable. All provided reports must be anonymized.

Follow-up reports relative to the patient's subsequent course must be submitted to [redacted] until the event has subsided or, in case of permanent impairment, until the condition stabilizes.

The Sponsor or its designated representative will report all the relevant safety information to the concerned Competent Authorities and to the Independent Ethics Committee(s) (IRB/IEC) concerned according to the country-specific requirements.

Investigator must fulfill his/her regulatory obligations to the Regulatory Authorities and/or to the Ethics Committee in accordance with local regulations.

Depending on local regulations in different regions and countries, the Sponsor or designated clinical research organization (CRO) may be required to expedite report to the Regulatory Authorities for:

- SAEs (including events related to study procedures)
- SADRs
- Suspected unexpected serious adverse reactions (SUSARs)

Each SAE report received from the Investigators will be evaluated by the designated CRO for pharmacovigilance who will assess the seriousness of the event. Each SAE report will be evaluated by the Sponsor and/or his designees who will assess the relationship to study procedure or study treatment and the expectedness of the event. Expectedness will be assessed using the reference safety information included in the Investigator Brochure.

Any unexpected safety issue that changes the risk benefit analysis and is likely to have an impact on the patients who have participated in the trial will be reported by the Sponsor as soon as possible to the Competent Authority(ies) concerned together with proposed actions.

8.3.3. Follow-up

The Investigator should take all appropriate measures to ensure the safety of the patients, notably he/she should follow up the outcome of any AE until the return to normal or until stabilization of the patient's condition.

The patient must be followed up until clinical recovery is complete and laboratory results have returned to normal, or until progression has been stabilized. This may imply that follow-up will continue after the patient has left the study and that additional investigations may be requested by the Sponsor. This information should be documented in the patient's medical records.

8.4. POST STUDY REPORTING REQUIREMENTS

Any SAEs and deaths that occur within 30 days of the last dose of the study drug, regardless of causality, should be reported.

Any SAE that is brought to the attention of the Investigator at any time after the reporting period and which is considered by him/her to be caused by the study drug within a reasonable possibility, should be reported.

8.5. CLINICAL LABORATORY ABNORMALITIES AND OTHER ABNORMAL ASSESSMENTS AS ADVERSE EVENTS OR SERIOUS ADVERSE EVENTS

Laboratory abnormalities are not necessarily recorded as AEs or SAEs. However, laboratory abnormalities that are considered clinically relevant by the Investigator must be recorded as an AE or SAE as applicable.

8.6. SPECIAL SITUATION REPORTS

Special situations reports include pregnancy reports, reports of medication error, abuse, misuse or overdose, and reports associated with product complaints.

8.6.1. Pregnancy

In case of pregnancy a communication will be sent by the Investigator to [redacted] by faxing a completed pregnancy form within 24 hours of his/her knowledge of the pregnancy.

Pregnancies of females partners of male patients exposed to study medication should also be reported to [redacted] using the corresponding pregnancy form, provided that pregnant female partners have signed an informed consent.

Female patients must be instructed to discontinue the study drug immediately and inform the Investigator as soon as possible once they are aware of being pregnant or suspect that they are pregnant during the study or within 30 days of the last dose of the study drug.

Female patients will be requested, as part of the general ICF, to provide informed consent to allow reasonable attempts to be made to obtain information on any possible medicinal product exposure to an embryo or fetus and to follow up on the outcome of the pregnancy.

The Investigator will contact the patient at the expected time of delivery for follow-up. If the outcome of pregnancy meets the criteria for immediate classification of an SAE (e.g., spontaneous or therapeutic abortion, stillbirth, neonatal death, congenital anomaly, birth defect), the Investigator should follow the procedure for reporting SAEs as detailed in Section 8.3.2.

The pregnancy itself is not considered an AE.

8.6.2. Medication error

Medication error is defined as an unintentional error in the prescribing, dispensing, or administration of a medicinal product while in the control of the healthcare professional, patient, or consumer. All medication errors will be documented in the eCRF and, in case of any potential risk to patient safety, would be reported as appropriate (see Section 8.3).

8.6.3. Misuse

This refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the authorized product information and will be reported in the eCRF. All misuse will be documented in the eCRF and, in case of any potential risk to patient safety, would be reported as appropriate (see Section 8.3).

8.6.4. Overdose

This refers to the administration of a quantity of a medicinal product given per administration or cumulatively, which is above the maximum recommended dose according to the authorized product information (see Section 8.1.1 and Section 8.3.1). Clinical judgment should always be applied.

8.6.5. Abuse

This corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

9. STATISTICAL METHODS AND DATA ANALYSIS

This section is an overview of the key elements of the statistical analysis for this study. Further details on statistical reporting and analyses will be contained in a separate statistical analysis plan (SAP). This SAP may be revised during the study only to accommodate protocol amendments and to make changes to adapt to unexpected issues in study execution and data collection that could affect planned analyses. In all circumstances, a final SAP should be issued prior to database lock and treatment unblinding. The first approved version of the SAP should be available within 3 months of first patient randomized and before the first DSMB meeting.

The main analyses will be based on patients with fibrosis stage F2 and F3. The summaries will be repeated in an exploratory manner with the inclusion of patients with fibrosis stage F1.

9.1. RANDOMIZATION AND TREATMENT ASSIGNMENT

Random allocation will be made to the 2 treatment groups (elafibranor and placebo) in a 2:1 ratio basis and stratified by the following factors:

- Type 2 diabetes (yes, no)
- Gender (male, female) (with a capping of women to 40%)
- Fibrosis stage (F1, F2, F3) (capped to 202 F1 patients).

Details on the randomization process are in Section 3.2.

9.2. ENDPOINTS

9.2.1. Surrogate endpoint - resolution of NASH

The first surrogate endpoint for this study is resolution of NASH without worsening of fibrosis after 72 weeks of treatment. Resolution of NASH is defined as the disappearance of ballooning (i.e., grade 0) and disappearance or persistence of minimal lobular inflammation (i.e., grade 0 or 1) with an overall pattern of injury not qualifying for steatohepatitis. Worsening of fibrosis is evaluated using NASH CRN fibrosis staging system and defined as progression of at least 1 stage. This surrogate endpoint will be formally assessed at the time of the surrogate efficacy analysis when at least the first 1023 randomized F2 and F3 patients complete the 72 week treatment period or discontinue early from the study treatment (see Section 9.8.1 for details). An additional exploratory analysis of this endpoint will take place at the time of the final analysis.

9.2.2. Long-term endpoint – time to clinical event/death

The long term endpoint of clinical outcomes is a composite endpoint composed of death due to any cause, histological liver cirrhosis, and the full list of portal hypertension/cirrhosis related events:

- Liver transplantation
- MELD score ≥15

- HCC
- the onset of:
    - variceal bleed
    - hepatic encephalopathy
    - spontaneous bacterial peritonitis
    - ascites
    - hepatorenal syndrome
    - hepatopulmonary syndrome
    - chronic gastrointestinal blood loss due to portal hypertensive gastropathy (provided that these lead to hospitalization or transfusion).

The final analysis will be performed when 456 patients experience an event listed above. This is expected to occur approximately 96 months after the first patient is randomized.

9.2.3. Key Secondary Endpoints

The key secondary endpoints are:

- Percentage of patients with improvement of fibrosis of at least 1 stage according to NASH CRN scoring at 72 weeks.

To assess the clinical benefit after 72 weeks of treatment on the following metabolic endpoints:

- Changes from baseline to Week 72 in triglycerides, Non-HDL cholesterol, HDL cholesterol, LDL cholesterol, HbA1c (in diabetic patients), HOMA-IR (in non-diabetic patients)

These key secondary endpoints will be assessed at the time of the surrogate endpoint analysis (at least the first 1023 randomized patients with fibrosis stage F2 and F3) for the resolution of NASH without worsening of fibrosis endpoint.

9.2.4. Other Secondary Endpoints

The other secondary endpoints are:

- To assess histological changes after 72 weeks of treatment and at the end of the LTTP on the following endpoints:
    - percentage of patients with resolution of NASH without worsening of fibrosis (at the end of LTTP)
    - percentage of patients with improvement of fibrosis of at least 1 stage according to NASH CRN scoring (at the end of LTTP)

  - percentage of patients with improvement of fibrosis of at least 1 stage according to NASH CRN scoring without worsening of NASH
  - percentage of patients with no worsening of Fibrosis and no worsening of NASH
  - percentage of patients with resolution of NASH and improvement of Fibrosis
  - percentage of patients with at least a 1 point improvement in histological scores (NASH CRN scoring: NAS [sum of steatosis, hepatic ballooning and lobular inflammation], steatosis, hepatic ballooning, lobular inflammation), fibrosis (NAFLD Ishak scoring system), or portal inflammation
  - percentage of patients with improvement of NAS of at least 2 points
  - percentage of patients with improvement of NAS of at least 2 points and with at least 1 point improvement in hepatic ballooning
  - percentage of patients with at least a 1 point improvement in disease activity score (sum of ballooning and lobular inflammation scores) according to NAS scoring and steatosis-activity-fibrosis (SAF) scoring
  - percentage of patients with at least a 1 point improvement in disease activity score (sum of ballooning and lobular inflammation scores) according to NAS scoring and with at least 1 point improvement in hepatic ballooning
  - percentage of patients with at least a 1 point improvement in disease activity score (sum of ballooning and lobular inflammation scores) according to steatosis-activity-fibrosis (SAF) scoring and with at least 1 point improvement in hepatic ballooning
  - percentage of patients with at least 2 points improvement in disease activity score according to NAS scoring and SAF scoring
  - changes in NAS, fibrosis (using NASH CRN and NAFLD Ishak scoring system), steatosis, hepatic ballooning, lobular inflammation, portal inflammation and SAF activity score
  - changes in area of fibrosis (normalized Collagen Proportional area in %) by morphometry.

- To assess the following endpoints at Week 72 and at the end of the LTTP:
  - changes in liver enzymes and liver markers
  - changes in noninvasive markers of fibrosis and steatosis
  - changes in lipid parameters
  - variation in body weight
  - changes in insulin resistance and glucose homeostasis markers
  - changes in inflammatory markers
  - changes in cardiovascular risk profile as assessed by Framingham scores
  - changes in liver stiffness by Fibroscan measurement
  - changes in quality of life (SF-36 questionnaire).
- To assess the onset to:
  - histological liver cirrhosis
  - death of any cause

- any portal hypertension or cirrhosis related events
- cardiovascular events
- liver-related death events.

9.2.5. Exploratory endpoints

The exploratory endpoint is:

- To constitute a biobank for discovery and validation of biomarkers in NASH.

Details on all endpoints will be given in the SAP.

9.3. ANALYSIS SETS

The following analysis sets will be used in this study:

- Enrolled: all patients who sign informed consent. This set will be used to summarize disposition.
- ITT: all randomized F2 and F3 patients. This set will be used to summarize efficacy. The main analysis of the primary and key secondary endpoints will be based on the ITT.
- Safety set (SS): all F2 and F3 patients who receive at least 1 dose of study drug. This set will be used to summarize safety.
- Efficacy evaluable set (EES): All F2 and F3 patients in the ITT population who have taken at least one dose of study treatment and have a reliable liver biopsy at both baseline and at the end of the 72 week treatment period.
- Per protocol set (PPS): all F2 and F3 patients who receive at least 1 dose of study drug and do not have any important protocol deviations leading to exclusion from the PPS. Important protocol deviations will be defined in the SAP and agreed prior to database lock. Supportive analysis of the primary and key secondary endpoints will be based on the PPS.
- Exploratory F1 cohort: All randomized F1 patients who have taken at least 1 dose of study drug.
- Full Intent-To-Treat Set (FITT): all randomized patients.
- Full Safety Set (FSS): all r patients who receive at least 1 dose of study drug.

Patients in the ITT, FITT, EES, PPS, and exploratory F1 cohorts (study population and efficacy data) will be analyzed based on randomized treatment. Patients in the SS, FSS, and exploratory F1 cohorts (safety data) will be analyzed based on actual treatment received.

9.4. ANALYSIS OF PRIMARY ENDPOINTS

9.4.1. Resolution of NASH

The null hypothesis for resolution of NASH without worsening of fibrosis is that there is no difference in response rates between the elafibranor and placebo groups. The alternative hypothesis is that there is a

difference in response rates between the elafibranor and placebo groups. The null hypothesis will be tested at the two-sided 0.01 alpha level.

The number and percentage of patients with resolution of NASH without worsening of fibrosis at the end of the 72 week treatment period will be summarized by treatment group. The main analysis will be performed using a logistic regression model, with fixed terms for treatment, type 2 diabetes (yes, no), gender (male, female), fibrosis stage (F2, F3) and baseline NAS. According to the method described in Ge et al. (2011)[36], the statistical model will be used to estimate the difference (elafibranor/placebo) in rate of resolution of NASH without worsening of fibrosis and its 99% CI. The main confirmatory analysis will be performed when at least the first 1023 randomized F2/F3 patients have completed the 72 week treatment period or discontinued early from the study treatment. The main analysis will be based on the ITT. Supportive analysis will be based on the EES and PPS.

Patients with missing data for resolution of NASH without worsening of fibrosis will be treated as a nonresponder for the main analysis. Supplementary analyses using multiple imputations and a pattern mixture model will be performed, as well as sensitivity analysis using a Cochran-Mantel-Haenszel test. Further details will be provided in the SAP.

9.4.2. Long-term endpoints

The null hypothesis is that there is no difference in the hazard ratio between the elafibranor and placebo treatment groups. The alternative hypothesis is that there is a difference in the hazard ratio between the elafibranor and placebo treatment groups. The null hypothesis will be tested at the two-sided 0.04 alpha level.

The data will be analyzed using a Cox proportional hazards model with fixed terms for treatment, type 2 diabetes, gender, fibrosis stage, and baseline NAS. The Cox proportional hazards model will be used to calculate the hazard ratio (elafibranor/placebo) and 96% confidence interval. This will be performed when at least 456 patients experience a clinical event/death. The time to clinical event/death will also be analyzed using an unadjusted Cox-proportional hazard's model, log rank test and a nonparametric randomization based analysis of covariance method proposed by Saville and Koch.[37]

The time to clinical event/death will be presented graphically using a Kaplan-Meier curve. The median time to first clinical event/death and 95% confidence interval will also be presented for each treatment group.

Missing data will be censored at the last known date.

The main analysis will be based on the ITT. Supportive analysis will be based on the EES and PPS.

9.5. OTHER STATISTICAL ANALYSIS

9.5.1. Key secondary endpoint

The number and percentage of patients with improvement of fibrosis according to NASH CRN scoring at the end of the 72 week treatment period will be summarized separately by treatment group. The data will be analyzed using a logistic regression model, with fixed terms for treatment, type 2 diabetes, gender, fibrosis stage and baseline NAS by NASH CRN scoring. The analysis will be performed at the time of the surrogate endpoint analysis when at least the first 1023 randomized patients with fibrosis stage F2 and F3 have completed the 72 week treatment period or discontinued early from the study treatment. The null hypothesis will be tested at the two-sided 0.01 alpha level.

The key secondary efficacy endpoints will be tested only if the primary surrogate endpoint is statistically significant. A gatekeeping procedure will be constructed to control the overall Type I error rate for testing the key secondary efficacy endpoints at an overall two-sided alpha level of 0.01.

The main analysis will be based on the IIT. Supportive analyses will be based on the EES and PPS.

9.5.2. Other secondary endpoints

All other secondary endpoints will be summarized by treatment group using descriptive statistics. The main analysis will be based on the ITT.

Categorical endpoints will be analyzed using a logistic regression model in the same manner as resolution of NASH without worsening of fibrosis.

Time to event endpoints such as time to first cardiovascular event/death will be analyzed using the Cox proportional hazard's model in the same manner as time to clinical event/death.

Continuous endpoints will be analyzed using a repeated measures Analysis of Covariance (ANCOVA) model with fixed terms for treatment, type 2 diabetes, gender, fibrosis stage, baseline NAS, and time-point and treatment by time-point interaction. A compound symmetry covariance matrix will be used for this analysis. The statistical model will be used to calculate the mean treatment difference and 95% confidence interval. If the data does not meet the required assumptions for parametric tests, the data will be analyzed using a nonparametric analysis of covariance method of Zink and Koch.[41]

Further details will be in the SAP.

9.5.3. Subgroup analyses

Exploratory analyses of the primary and key secondary endpoints will be done for selected subgroups, including, but not limited to, the following:

- Presence of type 2 diabetes (yes, no)
- Gender (male, female)
- Fibrosis (F2, F3)
- Geographic region (North America, Europe, South America, Rest of World)
- Race (Caucasian, Other)
- Ethnicity (Hispanic, not Hispanic)
- Age (<60, ≥60 years).
- PNPLA3 (absence or presence of risk allele G [i.e. CC vs GG/CG], and within the at risk group, homozygous vs. heterozygous for the risk allel G [i.e. CG vs GG])
- Patients under statins (yes/no), defined as patients who have duration of IP exposure greater or equal to 60 days, with extent of exposure to statin greater than or equal to 30 days before the visit 7 biopsy date.

Forest plots will be generated for each of these endpoints for patients in the ITT population.

9.5.4. Exploratory analyses

Additional exploratory analyses of the efficacy data will be performed on the exploratory F1 cohort and the FITT.

9.6. STRATEGIES TO CONTROL TYPE I ERROR

The overall type I error for the primary endpoints in this study is two-sided α=0.05. The alpha for the primary endpoints will be split 20%/80%, with two-sided α=0.01 for resolution of NASH and two-sided α=0.04 for time to clinical event/death.

The key secondary efficacy endpoints will be tested only if the primary surrogate endpoint is statistically significant at a two-sided 1% significance level. A gatekeeping procedure will be constructed to control the overall Type I error rate for testing the key secondary efficacy endpoints at an overall two-sided alpha level of 0.01.

The gatekeeping procedure will be detailed in the SAP and set up using the general method for building multi-stage parallel gatekeeping procedures in multiplicity problems with several families of null hypotheses (Dmitrienko and Tamhane, 2011, 2013).[38,39]

Statistical testing for all other secondary endpoints will be of exploratory nature.

As this is a single pivotal study that will be used for a regulatory submission, the consistency of the results for the primary and key secondary endpoints will be further explored by population and selected subgroups. In addition, different approaches will be applied for dealing with missing data.

9.7. SAMPLE SIZE CALCULATION

All sample size calculations were done in EAST 6.3.

9.7.1. Resolution of NASH

The following assumptions were made for the sample size calculation for resolution of NASH:

- α=0.01 two-sided
- Randomized patients with no response assessment at Week 72 will be counted as nonresponders
- Pooled variance
- Randomization ratio of 2:1 (elafibranor: placebo)
- 8% response in the control group
- 16.5% response in the elafibranor group.

The 8% response rate in the placebo group (calculated as the mean response rate based on the Phase II FLINT study[35] [subanalysis including only patients with stage 2 and stage 3 fibrosis or stage 1 fibrosis with diabetes, obesity or ALT ≥ 60 {associated with fibrosis progression}; placebo response rate 6.5%] and the GFT505-212-7 placebo data [11% response rate for patients with any stage fibrosis {F1; F2; F3} and 7% response rate for patients with only stage 2 and 3 fibrosis]). The 16.5% response rate in the elafibranor group is based on the Phase II GFT505-212-7 elafibranor data (calculated as the mean response rate based on a 20% response rate for patients with any stage fibrosis ([F1; F2; F3] and 13% response rate for patients with only stage 2 and 3 fibrosis).

Based on these assumptions, a sample size of at least 1023 patients provides 90% power to show that elafibranor is superior to the placebo with respect to resolution of NASH without worsening of fibrosis.

9.7.2. Time to clinical event/death

The following assumptions were made for the sample size calculation for time to clinical event/death:

- 24 month enrollment (with an 18-month ramp up to as many as 200 patients per month)
- 72 month maximum follow-up
- α=0.04 two-sided
- Annual event rate of 7% for the placebo group
- Hazard ratio of 0.75 in favor of the elafibranor group
- 4% annual drop-out rate over 72 months
- Randomization ratio of 2:1 (elafibranor: placebo).

The 7% annual event rate in the placebo group is based on published literature on developing cirrhosis in patients with NASH and advanced fibrosis (F2-F3).[21,22,23,24,25] The rate of developing cirrhosis was estimated to be 7% (based on 8% per year in F3 patients and 6% per year in F2 patients). In a conservative approach,

no additional event rate was added for other events than histological cirrhosis or cirrhosis decompensation events. An annual clinical event/death rate of 7% was thus defined for the composite of both these endpoints.

There is no long-term randomized clinical trial in a NASH population with moderate and severe liver fibrosis. In the 72-week FLINT trial, the total drop-out rate was 6.7%.[35] Therefore, we estimate an approximate annual drop-out rate of 4%. Based on these assumptions, 456 events are required to provide 80% power to show that elafibranor is superior to placebo with respect to time to clinical event/death. In order to obtain 456 events, at least 2022 patients will be required in the IIT.
The number of patients to be enrolled may be adjusted during the course of the study in a blinded manner to achieve the desired number of primary events. This will be accomplished using standard event forecasting methods (Anisimov, 2011).[40]

9.8. SAFETY ANALYSIS

Safety data (exposure, AEs, clinical laboratory tests, vital signs, and ECGs) will summarized by treatment group using descriptive statistics. The main summaries of safety will be based on the SS. Additional safety analysis will be based on the FSS and the exploratory F1 cohort.

Adverse events will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA). An overall summary of AEs will be provided. The number and percentage of patients reporting AEs will also be presented by MedDRA System Organ Class and preferred term. The AEs will be summarized by worst severity and relationship to study drug. Serious AEs, and AEs leading to discontinuation will also be summarized. Narratives will be added for all SAE.

Clinical laboratory tests (hematology, chemistry, and urinalysis) recorded at each timepoint and change from baseline will be summarized by treatment group using descriptive statistics. Clinical laboratory values for each parameter will be assigned a classification according to whether the value is lower than, within, or higher than the reference range for that parameter. The values will then be summarized using shift tables to evaluate categorical changes from baseline to end of the 72 week treatment period with respect to reference ranges. The number and percentage of patients reporting markedly abnormal clinical laboratory values will also be summarized by treatment group.

Liver and kidney related laboratory tests including an assessment of DILI will also be summarized.

Vital signs recorded at each timepoint and change from baseline will be summarized by treatment group using descriptive statistics.

9.8.1. Surrogate endpoint analysis

The analysis of resolution of NASH without worsening of fibrosis will occur when at least the first 1023 randomized F2 and F3 patients complete 72 weeks of treatment or discontinue early from the study treatment. The null hypothesis will be tested at the two-sided 0.01 alpha level.

At this time, a snapshot of the database will be cleaned and locked for analysis and potential Subpart H or conditional approval submission. This analysis will be done by an unblinded team separate from the study team; the study team will not be unblinded until the final analysis at the end of follow-up. A Data integrity plan will be set-up to detail the blinding/unblinding process and address how data will be published in view of marketing authorization and how integrity of the trial will be protected.

The DSMB will periodically review safety data from the study to ensure the well-being of study participants. One dedicated meeting will also be held upon availability of the surrogate endpoint analysis results.
DSMB will be provided with data summaries that will include selected efficacy results so that the DSMB can assess the likely benefit-risk profile of elafibranor. These are not considered a formal interim analysis, and no type I error adjustments will be done for these reviews. Details will be in the DSMB Charter.

9.9. INTERIM ANALYSIS

An adaptive design interim analysis will be performed after 140 primary events (approx. 30% of the 456 required events) have been accrued. The interim analysis will be performed by an unblinded team separate from the study team. The Data Safety Monitory Board (DSMB) will review the interim analysis results and provide final recommendations regarding trial termination due to futility and adjustment of the target number of primary events. Details will be in the DSMB Charter and SAP.

10. DATA HANDLING AND RECORD KEEPING

10.1. CASE REPORT FORM AND SOURCE DOCUMENTS

A case report form (CRF) is required and should be completed for each screened patient. The completed eCRFs are the sole property of the Sponsor and should not be made available in any form to third parties, except for authorized Sponsor's representatives or appropriate regulatory authorities, without written permission from the Sponsor.

The Investigator will ensure that all data are entered promptly, legibly, completely, accurately and conform to source documents, in accordance with specific instructions accompanying the eCRFs designed specifically for this study. The CRF being used for this study is an electronic CRF that has been fully certified as being compliant with the FDA regulations at 21 Code of Federal Regulations (CFR) Part 11.

All study required patient data generated during the study will be recorded in the eCRF, with the exception of SAE forms and SF-36 which will be collected via ePRO (which is then transferred to the electronic data capture). Patients will not be identified by name in the eCRF or on any study documents to be collected by the Sponsor (or designee), but will be identified by a patient number.

The Investigator will review and approve each completed eCRF; the Investigator's validation serving as attestation of the Investigator's responsibility for ensuring that all clinical and laboratory data entered in the eCRF are complete, accurate, and authentic.

Should a correction be made, the corrected information will be recorded in the eCRF by the authorized person and explained (if necessary). All corrected data will be tracked through an audit trail.

It is the Investigator's obligation to ensure documentation of all relevant data in the patient's medical file (medical history, concomitant diseases, patient identification number, date of informed consent, visit dates, administration of study medication, AEs [start and stop dates] and all concomitant medications [start and stop dates]). All data recorded in the eCRF will be documented by source data.

10.2. RETENTION OF RECORDS

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified.

The Investigator will be provided with a study file, which should be used to file the Investigator Brochure, protocol/amendments, drug accountability records, sample informed consent, staff curriculum vitae, correspondence with the IRB/IEC, Sponsor, and other study-related documents.

To enable evaluations and/or audits from regulatory authorities or the Sponsor, the Investigator agrees to keep records, including the identity of all participating patients, all original signed ICFs, copies of all eCRFs, source documents, and detailed records of treatment disposition.

The Investigator must retain the study documentation until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. However these documents should be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the Sponsor. All hospital records will be archived according to local regulation.

The Sponsor should be notified if the Investigator relocates, retires, or for any reason withdraws from the trial. The trial records must be transferred to an acceptable designee, such as another Investigator, another institution, or to the Sponsor.

11. QUALITY CONTROL AND QUALITY ASSURANCE

11.1. QUALITY CONTROL & MONITORING PROCEDURES

It is the responsibility of the Investigator to ensure that the study is conducted in accordance with the protocol, Good Clinical Practice (ICH topic E6), applicable regulatory requirements, and the current Declaration of Helsinki (APPENDIX I: World Medical Association Declaration of Helsinki) and that valid data are entered into the eCRFs.

To achieve this objective, the Study Monitor's duties are to aid the Investigator and, at the same time, the Sponsor in the maintenance of complete, legible, well-organized, and easily retrievable data.

Before enrolling any patients in this study, the Study Monitor will review the protocol, the brochure for clinical investigators, the eCRFs and instructions for their completion and return, the procedure for obtaining informed consent, and the procedure for reporting AEs and SAEs with the Investigator. In addition, the Study Monitor will explain the Investigator's reporting responsibilities and all applicable regulations concerning the clinical evaluation of the study drug.

The Investigator will permit the representatives of Sponsor to monitor the study as frequently as the Sponsor deems is necessary to determine that data recording and protocol adherence are satisfactory. A Study Monitor from [redacted] Late Stage Development Services will be responsible for monitoring this clinical trial. To this end, the Study Monitor will visit the study site at suitable intervals and be in frequent contact through verbal and written communication. The eCRFs and related source documents, as well as drug accountability will be reviewed in detail by the monitor at each visit, in accordance with relevant SOPs and Good Clinical Practice (GCP; ICH topic E6) regulations. This includes results of tests performed as a requirement for participation in this study and any other medical records required to confirm information contained in the eCRFs, such as past medical history and secondary diagnoses.

A risk based monitoring strategy will be used for this study. Study monitoring strategy design will be based on overall study risk assessment. Individual site monitoring strategy design will be based on individual site risk assessment. On site monitoring will focus on source document verification of mandatory and critical data and source document review of critical processes, and will be supported by formal remote site monitoring activities. Centralized monitoring activities will review study data to assess changes in individual site risk and to identify emerging trends, risks and issues across sites, countries, regions, and the global study. Further details can be found in the Monitoring Plan.

It is essential that the Study Monitor has access to all documents (related to the study and the individual participants) at any time these are requested. In turn, the Study Monitor will adhere to all requirements for patient confidentiality as outlined in the ICF. The Investigator and Investigator's staff will be expected to cooperate with the Study Monitor, to be available during a portion of the Monitoring Visit to answer questions, and to provide any missing information.

All monitoring activities will be reported and archived in the Trial Master File.

11.2. ETHICAL PRINCIPLES

This protocol complies with the principles laid down by the 18th World Medical Assembly (Helsinki, 1964) and all applicable amendments laid down by the World Medical Assemblies (APPENDIX I: World Medical Association Declaration of Helsinki), and the GCP guideline.

This trial also complies with applicable local regulatory requirements and laws of each country in which the study is performed, as well as any applicable guidelines.

11.3. QUALITY ASSURANCE

For the purpose of ensuring compliance with the protocol, GCP and applicable regulatory requirements, the Investigator should permit auditing by the Sponsor and/or designee and inspection by applicable regulatory authorities. The Investigator agrees to allow the auditors/inspectors to have direct access to his/her study records for review, being understood that these personnel will adhere to all requirements for patient confidentiality, and as such will not disclose any personal identity or personal medical information.

As soon as the Investigator is notified of a future inspection by the Authorities, he/she will inform the Sponsor and authorize the Sponsor to participate at this inspection.

The confidentiality of the data verified and the anonymity of the patients should be respected during these inspections.

Clinical data associates from the Sponsor's representative will review the data for completeness and logical consistency. Additionally, the clinical data associates will use automated validation programs to help identify missing data, selected protocol violations, out of range data, and other data inconsistencies. Requests for data clarification or correction will be electronically provided to the investigative site for resolution. Clinical data associates will assure that corrections have been applied properly.

12. ETHICS AND REGULATORY

12.1. INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE

The GCP guidelines and the US CFR Title 21 Section 56 (21 CFR 56) require that approval must be obtained from an Independent Ethics Committee (IRB/IEC) prior to participation of human patients in research studies. Prior to the study onset, the protocol, ICF, advertisements to be used for patient recruitment, and any other written information regarding this study to be provided to the patient or the patient's legally acceptable representative must be approved by the IRB/IEC. The Sponsor will supply relevant material for the Investigator to submit to the IRB/IEC for the protocol's review and approval. Verification of the IRB's unconditional approval of the protocol and the written ICF statement will be transmitted to the Investigator. Documentation of the relevant IRB/IEC approval and of the IRB/IEC compliance with GCP guideline will be maintained by the site and will be available for review by the Sponsor or its designee or by the authorized members of regulatory agencies.

The Applicant must supply the Sponsor with written documentation of the initial favorable opinion of the clinical research before the start of the trial.

The study will not commence until favorable opinion has been obtained from the appropriate IRB/IEC.

If any alterations, other than changes of administrative nature only, are made to the study protocol, a formal protocol amendment will be issued. The IRB/IEC will be informed by the Investigator of subsequent protocol amendments and of SUSARs. Approval for protocol amendments will be transmitted in writing to the Investigator.

The amendment will not be implemented until IRB/IEC approval, except in cases where immediate implementation is necessary to eliminate or prevent imminent hazard to the patients. A protocol change intended to eliminate an apparent immediate hazard must be documented in an amendment, reported to the IRC/IEC within 5 working days, and submitted to the appropriate regulatory agencies in the required time frame.

If requested, the Investigator will permit audits by the IRB/IEC and regulatory inspections by providing direct access to source data/documents.

The Investigator will provide the IRB/IEC with progress reports at appropriate intervals (not to exceed 1 year) and a Study Progress Report following the completion, termination, or discontinuation of the Investigator's participation in the study.

12.2. COMPETENT AUTHORITY

In the same way as for IRB/IEC (see Section 12.1), when required by national regulation, approval from Competent Authorities (CA) should be granted before the beginning of the study. If applicable, Amendments will also be submitted to CA for approval.

12.3. PATIENT INFORMATION AND CONSENT

Written informed consent for the study will be obtained from each patient before protocol-specific procedures are carried out. The ICF used by the Investigator for obtaining the patient's Informed Consent must be reviewed and approved by the Sponsor prior to submission to the appropriate ethics committee (IRB/IEC). The ICF will be approved (along with the protocol) by the IRB/IEC.

In the case of any exploratory substudies, specific study documents will be prepared and IRB/IEC and authority approvals shall be obtained when applicable.

The Investigator or a person designated by the Investigator (according to applicable regulatory requirements), will explain the nature of the study and the action of the test product. The patients will be informed that participation is voluntary and that they can withdraw from the study at any time. In accordance with 21 CFR 50, the informed consent process shall be documented by the use of a written ICF approved by the designated IRB/IEC and will be signed and personally dated by the patient or by the patient's legally acceptable representative and by the person who conducted the informed consent discussion prior to protocol-specific procedures being performed. A separate consent form will be obtained for optional genetic and biomarker samples to be stored in the blood bank.

The Investigator must maintain the original, dated and signed ICF. A copy of the signed ICF must be given to the patient.

12.4. PATIENT CONFIDENTIALITY

The Sponsor will affirm and uphold the principle of the patient's right to protection against the invasion of privacy. Throughout this study and any subsequent data analyses, all data will be identified only by protocol number and patient number.

All unpublished information that the Sponsor gives to the Investigator shall be kept confidential and shall not be published or disclosed to a third party without the prior written consent of the Sponsor.

When the Sponsor generates reports for presentations to regulatory agencies, one or more of the Investigators who has/have contributed significantly to the study will be asked to endorse the final report. The endorsement is required by some regulatory agencies.

The Investigator shall not make a patent application based on the results of this study and shall not assist any third party in making such an application without the written authorization of the Sponsor unless otherwise specified in the CSA.

12.5. DEFINITION OF THE END OF THE RESEARCH

End of the research corresponds to the end of participation (end of study EOT Visit) of the last patient participating in the research.

13. FINANCING AND INSURANCE

13.1. FINANCIAL ISSUES

Financial contracts will be signed between the Sponsor and the Investigator/Institution before initiation of the study.

13.2. INSURANCE AND PATIENT INJURY

The patients taking part in the trial will be covered by the insurance taken by the Sponsor for this trial, if they were to suffer any prejudice as a result of taking part in the trial.

In general, if a patient is injured as a direct result of the study drug, the Sponsor will pay for reasonable and necessary medical treatment for the injury, to the extent the expenses are not covered by the patient's medical insurance, a government program, or other responsible third party. If laws or regulations of the locality in which the trial is taking place require additional payment of expenses, the Sponsor shall comply with such law or regulation.

The Sponsor certifies to have taken out an insurance policy to cover the financial consequences of its civil liability and that of everyone involved in the research, and notably that of the Investigators and their colleagues with regard to any accidents or damage concerning the administration of the drug or paraclinical examinations directly linked to the performance of the trial.

14. STUDY RESULTS AND PUBLICATION POLICY

14.1. STUDY REPORT

The final report will be written in ENGLISH upon completion of study and statistical analysis according to ICH E3 guideline. The report or part of it must be submitted to relevant authorities if applicable.

[redacted] will prepare an integrated clinical and safety report. Prior to issuing the final CSR, [redacted] will prepare a draft report for approval by the Sponsor. The report will be in accordance with the ICH E3 Guideline for Industry: Structure and Content of CSRs. The draft report will be submitted for Quality Assurance audit, the findings of which will be incorporated into the final version.

An electronic copy of the final CSR will be made available to the Sponsor. The study report will be provided in PDF and MS Word formats unless agreed otherwise by [redacted] Reports requiring specialized Sponsor formats/alternative computer software packages may be possible on request from the Sponsor but may involve extra time and cost. Electronic datasets will also be provided to the Sponsor on issuance of the final report.

After review by the Sponsor, a final CSR will be submitted to the Sponsor which incorporates the Sponsor's comments.

14.2. CONFIDENTIALITY AND OWNERSHIP OF DATA, USE OF THE STUDY RESULTS AND PUBLICATION

All materials, information (oral or written), and unpublished documentation provided to the Investigators (or any company/institution acting on their behalf), including this protocol, the patient CRFs, and the Investigator's Brochure, are the exclusive property of the Sponsor and may not be published, given, or disclosed, either in part or in whole, by the Investigator or by any person under his/her authority to any third party without the prior express consent of the Sponsor.

However, the submission of this protocol and other necessary documentation to the ethics committee (IRB/IEC) and the Competent Authority is expressly permitted, their members having the same obligation of confidentiality.

The Investigator shall consider all information, results, discoveries, records (accumulated, acquired, or deduced) in the course of the study, other than that information to be disclosed by law, as confidential and shall not disclose any such results, discoveries, or records to any third party without the Sponsor's prior written consent.

The Sponsor retains exclusive ownership of all data, results, reports, findings, discoveries, and any other information collected during this study. Therefore, the Sponsor reserves the right to use the data from the present study, either in the form of Case Report Forms (or copies of these), or in the form of a report, with

or without comments and with or without analysis, in order to submit them to the Health Authorities of any country.

When the Sponsor generates reports for presentations to regulatory agencies, one or more of the Investigators who has/have contributed significantly to the study will be asked to endorse the final report. The endorsement is required by some regulatory agencies.

Furthermore, in the event that the study generates patentable results, the Investigator (or entity acting on his/her behalf according to local requirements) shall refrain from filing patent application(s) on such results, which will be filed by the Sponsor or its designees in its own name and at its expense.

Clinical study will be registered on the open access website http://www.clinicaltrials.gov before the screening of the first patient in the study.

It is the policy of the Sponsor to encourage the presentation and/or publication of the results of their studies, using only clean, checked, and validated data in order to ensure the accuracy of the results.

The publication of study results will be agreed between the Sponsor and the Investigators.

At least 45 days in advance of proposed submission, the Investigator should forward a copy of the manuscript or abstract for review by the Sponsor, and, if necessary, delay publication or communication for a limited time in order to protect the confidentiality or proprietary nature of any information contained therein. The Sponsor may also request that the Sponsor's name and/or names of one or several of its employees appear or not appear in such publication.

15. REFERENCES LIST

1. Day CP, James OF. Steatohepatitis: a tale of two "hits"? *Gastroenterology*. 1998;114:842-845.
2. Jou J, Choi SS, Diehl AM. Mechanisms of disease progression in nonalcoholic fatty liver disease. *Semin Liver Dis*. 2008;28: 370-379.
3. Edmison J, McCullough AJ. Pathogenesis of nonalcoholic steatohepatitis: human data. *Clin Liver Dis*. 2007;11:75-104.
4. Browning JD, Horton JD. Molecular mediators of hepatic steatosis and liver injury. *J Clin Invest*. 2004;114:147-152.
5. Ikejima K, Honda H, Yoshikawa M, et al. Leptin augments inflammatory and profibrogenic responses in the murine liver induced by hepatotoxic chemicals. *Hepatology*. 2001;34: 288-297.
6. Poniachik J, Santibanez C, Haim D, et al. Enhancement in liver nuclear factor-kb (NF-KB) and activator protein 1 (AP-1) DNA binding in obese patients with nonalcoholic fatty liver disease. The 43rd Annual Meeting of the European Association for the Study of the Liver. Milan, Italy, 2008.
7. Yamauchi T, Kamon J, Minokoshi Y, et al. Adiponectin stimulates glucose utilization and fatty-acid oxidation by activating AMP-activated protein kinase. *Nat Med*. 2002;8(11):1288-95. Epub 2002 Oct 7.
8. Targher G, Bertolini L, Rodella S, et al. Associations between plasma adiponectin concentrations and liver histology in patients with nonalcoholic fatty liver disease. *Clin Endocrinol (Oxf).* 2006;64:679-683.
9. Xu H, Barnes G, Yang Q, et al. Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance. *J Clin Invest*. 2003;112(12):1821-1830.
10. Pessayre D, Fromenty B, Mansouri A. Mitochondrial injury in steatohepatitis. *Eur J Gastroenterol Hepatol*. 2004;16:1095-1105.
11. Crespo J, Cayon A, Fernandez-Gil P, et al. Gene expression of tumor necrosis factor alpha and TNF-receptors, p55 and p75, in nonalcoholic steatohepatitis patients. *Hepatology*. 2001;34:1158–1163.
12. Hotamisligil GS, Arner P, Caro JF, et al. Increased adipose tissue expression of tumor necrosis factor-alpha in human obesity and insulin resistance. *J Clin Invest.* 1995;95:2409-2415.
13. Ramalho RM, Cortez-Pinto H, Castro RE, et al. Apoptosis and Bcl-2 expression in the livers of patients with steatohepatitis*. Eur J Gastroenterol Hepatol*. 2006;18:21-29.
14. Laurin J, Lindor KD, Crippin JS, et al. Ursodeoxycholic acid or clofibrate in the treatment of nonalcohol-induced steatohepatitis: a pilot study. *Hepatology*. 1996;23(6):1464-1467.
15. Shan W, Nicol CJ, Bility MT, et al. Peroxisome proliferator-activated receptor-beta/delta protects against chemically induced liver toxicity in mice, *Hepatology*. 2008;47(1):225-235.
16. Risérus U, Sprecher D, Johnson T, et al. Activation of peroxisome proliferator-activated receptor (PPAR) delta promotes reversal of multiple metabolic abnormalities, reduces oxidative stress,

and increases fatty acid oxidation in moderately obese men. *Diabetes*. 2008;57(2):332-339. Epub 2007 Nov 16.

17. Kang K, Reilly SM, Karabacak V, et al. Adipocyte-derived TH2 cytokines and myeloid PPAR delta regultate macrophage polarization and insulin sensitivity. *Cell Metab.* 2008;7:485-495.
18. Odegaard JI, Ricardo-Gonzalex RR, Red Eagle A et al. Alternative M2 activation of Kupffer cells by PPARδ ameliorates obesity induced insulin resistance. *Cell Metab*. 2008;7:496-507.
19. Cattley RC, Deluca j, Elcombe C, et al. Do peroxisome proliferating compounds pose a hepatocarcinogenic hazard to humans? *Regul Toxicol Pharmacol*. 2008;27(1 Pt 1):47-60.
20. Musso G, Gambino R, Cassader M, Pagano G . Meta-analysis: natural history of nonalcoholic fatty liver disease (NAFLD) and diagnostic accuracy of non-invasive tests for liver disease severity. *Ann Med*. 2011;43(8):617-649.
21. Ekstedt M, Franzen LE, Mathiesen UL, et al. Long-term follow-up of patients with NAFLD and elevated liver enzymes. *Hepatology.* 2006;44(4):865-873.
22. Angulo P, Kleiner DE, Dam-Larsen S, et al. Liver Fibrosis, but No Other Histologic Features, Is Associated With Long-term Outcomes of Patients With Nonalcoholic Fatty Liver Disease. *Gastroenterology.* 2015;149(2):389-397 e310.
23. Argo CK, Northup PG, Al-Osaimi AM, Caldwell SH . Systematic review of risk factors for fibrosis progression in nonalcoholic steatohepatitis. *J Hepatol*. 2009;51(2):371-379.
24. Pagadala MR, McCullough AJ. The relevance of liver histology to predicting clinically meaningful outcomes in nonalcoholic steatohepatitis. *Clin Liver Dis* 2012;16(3):487-504.
25. Singh S, Allen AM, Wang Z, Prokop LJ, Murad MH, Loomba R. Fibrosis progression in nonalcoholic fatty liver vs nonalcoholic steatohepatitis: a systematic review and meta-analysis of paired-biopsy studies. *Clin Gastroenterol Hepatol.* 2015;13(4):643-654.
26. Hashimoto E, Tokushige K. Prevalence, gender, ethnic variations, and progression of NASH. *J Gastroenterol.* 2011;46(supplement 1):63-69.
27. Younossi ZM, Stepanova M, Rafiq N, et al. Pathologic criteria for nonalcoholic steatohepatitis: interprotocol agreement and ability to predict liver-related mortality. *Hepatology.* 2011;53(6):1874-1882.
28. Ratziu V, de Ledinghen V, Oberti F, et al. A randomized controlled trial of high-dose ursodesoxycholic acid for nonalcoholic steatohepatitis. *J Hepatol.* 2011;54(5):1011-1019.
29. Sanyal AJ, Brunt EM, Kleiner DE, et al. Endpoints and clinical trial design for nonalcoholic steatohepatitis. *Hepatology*. 2011;54:344-353.
30. Sanyal AJ, Friedman SL, McCullough AJ, et al. Challenges and opportunities in drug and biomarker development for nonalcoholic steatohepatitis: findings and recommendations. *Hepatology.* 2015;61(4):1392-1405.
31. McPherson S, Hardy T, Henderson E, et al. Evidence of NAFLD progression from steatosis to fibrosing-steatohepatitis using paired biopsies: implications for prognosis and clinical management. *J Hepatol*. 2015;62(5):1148-1155.

32. Dunn W, Xu R, Wingard DL, et al. Suspected nonalcoholic fatty liver disease and mortality risk in a population-based cohort study. *Am J Gastroenterol.* 2008;103(9):2263-2271.
33. Rafiq N, Bai C, Fang Y, et al. Long-term follow-up of patients with nonalcoholic fatty liver. *Clin Gastroenterol Hepatol.* 2009;7(2):234-328.
34. Clinical Trial Facilitation Group (2014). Recommendations related to contraception and pregnancy testing in clinical trials. Available at: http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf
35. Neuschwander-Tetri BA, Loomba R, Sanyal AJ, et al. Farnesoid X nuclear receptor ligand obeticholic acid for non-cirrhotic, nonalcoholic steatohepatitis (FLINT): a multicentre, randomised, placebo-controlled trial. *Lancet*. 2015;385(9972):956-965.
36. Ge, M., Durham, L. K., Meyer, R. D., Xie, W., & Thomas, N. (2011). Covariate-adjusted difference in proportions from clinical trials using logistic regression and weighted risk differences. *Drug Information Journal*, *45*(4), 481-493.
37. Saville RS and Koch G. Estimating Covariate-Adjusted Log Hazard Ratios in Randomized Clinical Trials Using Cox Proportional Hazards Models and Nonparametric Randomization Based Analysis of Covariance. Journal of Biopharmaceutical Statistics. 2013 23: 477-490.
38. Dmitrienko, A., Tamhane, A.C. Mixtures of multiple testing procedures for gatekeeping applications in clinical trials. Statistics in Medicine. 2011 30: 1473-1488.
39. Dmitrienko, A., Tamhane, A.C. General theory of mixture procedures for gatekeeping. Biometrical Journal. 2013 55: 402-419.
40. Anisimov, V. Predictive event modelling in multicentre clinical trials with waiting time to response. Pharmaceutical Statistics. 2011; 10, 517-522.
41. Zink RC and Koch G. NParCov3: A SAS/IML Macro for Nonparametric Randomization-Base Analysis of Covariance. Journal of Statistical Software. 2012 July 50:3.

Appendices

APPENDIX I: WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

APPENDIX II: ADEQUATE DIET AND LIFESTYLE RECOMMENDATIONS

Essential Components of Therapeutic Lifestyle Changes (TLC)

Component	Recommendation
LDL-raising nutrients	
Saturated fats*	Less than 7% of total calories
Dietary cholesterol	Less than 200 mg/day
Therapeutic options for LDL lowering	
Plant stanols/sterols	2 grams per day
Increased viscous (soluble) fiber	10–25 grams per day
Total calories (energy)	Adjust total caloric intake to maintain desirable body weight/prevent weight gain
Physical activity	Include enough moderate exercise to expend at least 200 kcal per day

* *Trans* fatty acids are another LDL-raising fat that should be kept at a low intake.

Macronutrient Recommendations for the TLC Diet

Component	Recommendation
Polyunsaturated fat	Up to 10% of total calories
Monounsaturated fat	Up to 20% of total calories
Total fat	25–35% of total calories*
Carbohydrate†	50–60% of total calories*
Dietary fiber	20–30 grams per day
Protein	Approximately 15% of total calories

* ATP III allows an increase of total fat to 35 percent of total calories and a reduction in carbohydrate to 50 percent for persons with the metabolic syndrome. Any increase in fat intake should be in the form of either polyunsaturated or monounsaturated fat.
† Carbohydrate should derive predominantly from foods rich in complex carbohydrates including grains—especially whole grains—fruits, and vegetables.

APPENDIX III: PERMITTED/NON-PERMITTED MEDICATION

Table I: NON-PERMITTED MEDICATION AND CONDITION

Medications	**When**
Same pharmacological class (PPAR agonists)	
Thiazoledinediones (glitazones [pioglitazone and rosiglitazone])	From 6 months prior to diagnostic liver biopsy* up to end of study treatment (EOT) Visit
Fibrates	From 2 months prior to Randomization up to EOT Visit
Medication that may induce steatosis/steatohepatitis	
Corticosteroids (parenteral & oral chronic administration)	From 30 days prior to first Screening Visit up to EOT Visit
Amiodarone	
Tamoxifen	
Methotrexate	
Medication that may interact with absorption, metabolism, etc	
Indomethacin	From Randomization up to EOT Visit

* Given the potential effect on diagnostic liver biopsy of patients previously treated by glitazones

Table II: PERMITTED MEDICATION AND CONDITION

Medications	When
Antidiabetic therapy	
GLP-1 agonist	Dose stability required in the 6 months prior to the diagnostic liver biopsy No qualitative change (i.e., no initiation of a new drug) from at least 6 months prior to the diagnostic liver biopsy up to 72-week of treatment (V7). Dose changes after randomization should be avoided
All other ATD therapy (insulin, sulfonylureas, metformin, gliptins)	No qualitative change (i.e., no initiation of a new drug) from at least 6 months prior to the diagnostic liver biopsy and up to Randomization (Dose changes are allowed). Dose changes after randomization are allowed.
SGLT2-inhibitors	No qualitative change (i.e., no implementation of a new drug) from at least 6 months prior to the diagnostic liver biopsy up to 72-weeks of treatment (V7). Dose changes after randomization should be avoided.
Lipid lowering therapy	
Statins	Dose stability required from at least 2 months prior to Screening. Dose changes are allowed after Randomization if judged necessary by the physician
Ezetimibe	
Other nonfibrate lipid lowering therapies	
Others	
Vitamin E >400 IU/day	Dose stability required from at least 6 months prior to the diagnostic liver biopsy. Dose changes should be avoided up to EOT
PUFAs >2 g/day	
Ursodeoxycholic acid	

Abbreviations: ATD = autoimmune thyroid disease; EOT = end of study treatment; GLP-1 =glucagon-like peptide 1; PUFA = polyunsaturated fatty acids; SGLT2 = sodium/glucose cotransporter 2.

APPENDIX IV: ALCOHOL COMPARISON TABLE

Alcohol type	**Alcohol by volume (ABV)**	**Volume**		**Amount of alcohol**	
		Fluid ounce	**mL**	**Units** 2	**grams**
Beer	3.5%	12	350	0.7	9.8
Beer	5%	12	350	1	14
Cider	7%	12	350	1.4	19.6
Distilled spirits or liquor 1	40%	1.5	45	1	14
Wine	12%	5	150	1	14

1. e.g., gin, rum, vodka, whiskey.
2. Units calculated using the cleave Books calculator for units of drink, using the US definition of 1 unit of alcohol as 17.7 mL (14.0 g) of pure alcohol (http://www.cleavebooks.co.uk/scol/ccalcoh3.htm).

APPENDIX V: PRODUCT CARTON AND WALLET LABELING

	Carton	Wallet
Protocol number	X	X
Sponsor details	X	X
Site number	X	-
Subject ID	X	X
Kit number	X	X
Visit number	X	-
Lot number	X	X
Expiry date	X	X
Contents	X	X
Route of administration	X	X
Administration instructions	X	X
"For Clinical Trial Use only."	X	X
"Keep out of reach of Children."	X	X
Storage details	X	X
Instructions for product and package return at next visit	X	X

CLINICAL PROTOCOL – PHASE 3

Protocol N° GFT505-315-1

EudraCT N°2015-005385-38

IND number: 115028

Amendment 4: Final 5.0– Release date 20 April 2020

Supersedes previous Version 4.0 - Release date: 03 January 2020

USA: Supersedes previous Version 4.2 - Release date: 09 April 2020

[redacted]

International Coordinating Investigator Committee	[redacted]	
Sponsor	**GENFIT**	Parc Eurasanté 885, Avenue Eugène Avinée 59120 LOOS, France
Represented by:	[redacted]	[redacted]

CLINICAL STUDY PROTOCOL SIGNATURE PAGE

Protocol N°: **GFT505-315-1 / EudraCT N° 2015 - 00 5385- 38 / IND n°115028**

Version number: **5.0**

Release date: **20 April 2020**

TITLE: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Phase III Study to Evaluate the Efficacy and Safety of Elafibranor in Patients with Nonalcoholic Steatohepatitis (NASH) and fibrosis.

In signing below, I give agreement to the protocol.
International Coordinators:

[redacted]

[redacted]

Signature

[redacted]

Date (dd-mmm-yyyy)

CLINICAL STUDY PROTOCOL SIGNATURE PAGE

Protocol N°: **GFT505-315-1 / EudraCT N° 2015-005385-38/ IND n°115028**

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In signing below, I give agreement to the protocol.
International Coordinators:

[redacted]

Signature

[redacted]

Date (dd-mmm-yyyy)

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In signing below, I give agreement to the protocol.
International Coordinators:

[redacted]

Signature

[redacted]

Date (dd-mmm-YWY)

CLINICAL STUDY PROTOCOL SIGNATURE PAGE

Protocol N°: **GFT505-315-1 / EudraCT N° 2015-005385-38/ IND n°115028**

Version number: **5.0**

Release date: **20 April 2020**

TITLE: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Phase III Study to Evaluate the Efficacy and Safety of Elafibranor in Patients with Nonalcoholic Steatohepatitis (NASH) and fibrosis.

In signing below, I give agreement to the protocol.

On behalf of (the Sponsor): GENFIT
Parc Eurasanté
885, Avenue Eugène Avinée
59120 LOOS – France

Name: [redacted]

[redacted]

Signature *Date (dd-mmm-yyyy)*

CLINICAL STUDY PROTOCOL
INVESTIGATOR SIGNATURE PAGE

PROTOCOL TITLE: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Phase III Study to Evaluate the Efficacy and Safety of Elafibranor in Patients with Nonalcoholic Steatohepatitis (NASH) and fibrosis.

PROTOCOL NUMBER: GFT505-315-1

EudraCT Number: 2015-005385-38

IND Number: 115028

CLINICAL PHASE: III

VERSION: 5.0

DATE: 20 April 2020

SPONSOR: GENFIT,
Parc Eurasanté,
885 Avenue Eugène Avinée,
59120 LOOS - France

In signing below, I confirm having read the protocol, and give agreement to the protocol.

INVESTIGATOR NAME: _____

INSTITUTION NAME: _____

INSTITUTION ADDRESS: _____

_____

SIGNATURE: _____

DATE: _____/_____/_____

Day Month Year

STUDY CONTACTS

Protocol N°: GFT505-315-1/ EudraCT N° 2015-005385-38/ IND n° 115028

International Coordinating Investigator Committee	[redacted]	[redacted]
Sponsor	GENFIT	Parc Eurasanté 885, Avenue Eugène Avinée 59120 LOOS - France
CRO for monitoring, data management & statistics	[redacted]	[redacted]
Pharmacovigilance	[redacted]	[redacted]


IXRS
Study drug supplier
Central laboratory
Central pathology laboratory
ePRO

SUMMARY OF CHANGES
AMENDMENT 4: 2020

Amendment 4 is a substantial change to address the change in definition of the primary clinical benefit endpoint and associated adjudication process. In addition, updates have been made to clarify the criteria to be used to identify patients with potential DILIs. A list of adverse events of special interest has also been added and clarification made on the required follow-up of the potential treatment related adverse events.
An additional section has been added to address the optional solutions put in place in case a patient participating in the RESOLVE-IT study cannot attend a site visit during the COVID-19 crisis or future crisis situation.

Added text is **bolded**; deleted text is ~~struck through~~.

Summary of major changes to the protocol:

Section	**New Text**
Section 1.9.2	Primary endpoint events include overall mortality, progression to cirrhosis, and the full list of portal hypertension/cirrhosis related events (liver transplantation, model end stage liver disease (MELD) score ≥15, ~~hepatocellular carcinoma (HCC),~~ and hospitalization due to occurrence of hepatic encephalopathy~~,~~ **or** variceal bleeding, spontaneous bacterial peritonitis, **and** uncontrolled ascites **requiring treatment)**~~, hepatorenal syndrome, hepatopulmonary syndrome, and chronic gastrointestinal blood loss due to portal hypertensive gastropathy [provided that these lead to hospitalization or transfusion])~~.
Section 2.1.2	To evaluate the efficacy of elafibranor 120 mg QD versus placebo on clinical outcomes described as a composite endpoint composed of death due to any cause, histological liver cirrhosis, and the full list of portal hypertension/cirrhosis related events: • Liver transplantation • MELD score ≥15 **for patients with baseline MELD score ≤12** • ~~HCC~~ • the onset of: o ~~variceal bleed~~ **requiring hospitalization,** o ~~hepatic encephalopathy~~ **defined as West Haven/Conn score ≥2 and requiring hospitalization,** o ~~spontaneous bacterial peritonitis~~**,** o ~~ascites~~ **requiring treatment.**

	~~hepatorenal syndrome~~ ~~o hepatopulmonary syndrome~~ ~~o chronic gastrointestinal blood loss due to portal hypertensive gastropathy (provided that these lead to hospitalization or transfusion).~~
Section 2.6	To assess the tolerability and safety of once a day administration of oral doses of elafibranor 120 mg: • SAE, AE, **AESI,** physical examination, vital signs, medical history, ECG • hematological parameters • liver markers • renal biomarkers (including urinalysis) • cardiac biomarkers • metabolic parameters • other biochemical safety markers.
Section 3.10	Patients who have permanently discontinued study drug due to an event listed in the primary composite endpoint for long-term efficacy described in Section 1.9.2 will be discontinued from the study following the EOT Visit and have no further follow-up**, unless the patient experiences at the time of EOT visit, an ongoing adverse event possibly related to study treatment for which the follow-up should last until resolution of this adverse event**. Patients who have permanently discontinued study drug for any other reason will remain, upon agreement, in the study and will be followed up with phone visits every 24 weeks (±2 weeks from EOT Visit) following the EOT Visit to report safety, diagnosis of cirrhosis and occurrence of clinical outcomes (as listed below) including liver and cardiovascular events until EOS or the occurrence of an event listed in the primary composite endpoint for long-term efficacy (described in Section 1.9.2), whichever is sooner. The following procedures will be performed during the follow-up phone visit for patients who have permanently discontinued study drug: • IXRS registration.

	• Reporting of safety information regarding: ○ any new AEs ○ resolution of previous AEs ○ change in severity of existing AEs ○ occurrence of any cardiovascular events ○ occurrence of diabetes (for patients not previously diagnosed with diabetes) ○ worsening of diabetes (for patients previously diagnosed with diabetes). • Reporting of any change in diet and life style factors • Reporting of any change (quantitative or qualitative) in therapies post study drug discontinuation • Reporting of cirrhosis diagnosis (patient to be asked if they have had any histological confirmation of cirrhosis) • Reporting of any of the following events (primary composite endpoint for long-term efficacy evaluation): ○ liver transplantation ○ MELD score ≥15 **for patients with baseline MELD score ≤12** ○ ~~HCC~~ ○ the onset of: ▪ variceal bleed **requiring hospitalization** ▪ hepatic encephalopathy **defined as West Haven/Conn score ≥2 and requiring hospitalization** ▪ spontaneous bacterial peritonitis ▪ ascites **requiring treatment.** ▪ ~~hepatorenal syndrome~~ ▪ ~~hepatopulmonary syndrome~~ ▪ ~~chronic gastrointestinal blood loss due to portal hypertensive gastropathy (provided that these lead to hospitalization or transfusion).~~ ○ death due to any cause.
Section 3.12 (changes from protocol version 4.0)	**3.12 -OFF-SITE STUDY PROCEDURES IN CASE OF CRISIS SITUATION** **Based on assessment of risk, and to ensure patient safety and minimize risks to trial integrity, the sponsor determined that the following optional off-site study procedures can be performed in case a study participant cannot attend an on-**

site visit during the COVID-19 crisis:

Safety assessment via phone call
Local lab assessment
Delivery of the study treatment to patient
Visit to patient's home

These options apply to all on-site study visits except for the randomization visit (Visit 1). Visit 1 must occur on-site as per section 3.7.1.

These solutions can be applied depending on the investigator's judgment of each case and the patient's agreement. The alternative solutions can be implemented in response to the COVID-19 crisis prior to the notification or submission to and approval of regulatory agencies and ethics committees.

Before implementing any of these options for a patient, the site will contact the patient to check whether he/she agrees with the off-site procedures.

The patient will be invited to attend an on-site visit to complete the study procedures as per protocol, as soon as the situation allows it.

In cases of any future emergency (e.g., pandemic, political strife, natural disasters), to continue to ensure patient safety and minimize risks to trial integrity, after completion of a risk assessment similar measures could be taken.

3.12.1 Safety and drug compliance procedures

The following procedures will be performed via either a phone contact, or, if safe and possible, a direct visit to the patient:

- **Check for AEs and occurrence of any clinical outcome (described in Section 6 and Section 8)**
- **Report any change in diet and life style factors**
- **Check concomitant/prior medication (described in Section 7.12 and APPENDIX III: Permitted/non-permitted medication)**
- **Record result of home pregnancy tests (to be performed every 4 weeks [see Figure 2]) since previous visit (for WOCBP only, every visit from V1)**
- **Drug accountability**
  - **dates of any study drug interruption since the last dispensation and reason***
  - **end of treatment (if applicable): date of last dose of study drug and reason***
  - **end of study (if applicable) : date of end of study and reason***

***if the reason is related to an AE, collect all required details**

- **Physical examination if possible with a direct visit to the patient (described in Section 6.2.1)**

	• **Record vital signs and weight if possible with a direct visit to the patient (described in Section 6.2.1 and Section 6.2.3)** • **Based on the study visit period for the patient, excluding the quality of life assessment, additional protocol related procedures of Section 3.7.2 or Section 3.8.1 may be performed if possible and if necessary conditions are met** **3.12.2 Local lab assessment** **The patient will be asked if he/she can access a local lab in the few days after the phone contact to obtain hematology, biochemistry and urinalysis testing.** **If a direct visit to the patient is safe and possible, the appropriate lab parameters corresponding to the on-site study visit as described in Table 2 will be collected.** **3.12.3 Delivery of study treatment to the patient** **The IXRS registration will be completed to trigger study drug kit assignments, and the assigned drug kits can be shipped to the patient, or delivered directly to the patient by the site study staff if safe and possible.** **As per the usual study visit, the patient will be instructed to continue taking the available tablets from the existing kit until he/she receives the new kit.** **The study drug compliance and study drug accountability will be performed as described in Section 7.10 and Section 7.11 once brought to the study site/study pharmacy.** **3.12.4 Completion of Missed Study Procedures** **As soon as the situation allows it, the site will schedule the patient's on-site visit to complete the missed study procedures (those that could not be performed during the phone calls/visit to patient) as per protocol (see Section 3.7.2 or Section 3.8.1).**
Section 3.12 (changes from Protocol version 4.2 –US specific)	These solutions can be applied depending on the investigator's judgment of each case and the patient's agreement. **The alternative solutions can be implemented in response to the COVID-19 crisis prior to the notification or submission to and approval of regulatory agencies and ethics committees.** Before implementing any of these options for a patient, the site will contact the patient to check whether he/she agrees with the off-site procedures. The patient will be invited to attend an on-site visit to complete the study procedures as per protocol, as soon as the situation allows it.

	In cases of any future emergency (e.g., pandemic, political strife, natural disasters), to continue to ensure patient safety and minimize risks to trial integrity, after completion of a risk assessment similar measures could be taken.
Section 5.2.2	If the study drug is discontinued due to the occurrence of any event listed in the composite endpoints for long-term efficacy evaluation (see Section 1.9.2), the patient will also be discontinued from the study with no further follow-up after the EOT Visit**, unless the patient experiences at the time of EOT visit, an ongoing adverse event possibly related to study treatment for which the follow-up should last until resolution of this adverse event**.
Section 5.2.3	Where possible, patients withdrawn from the study will be followed until resolution of all their SAEs or **possibly related AEs** until the unresolved SAEs **or possibly related AEs** are judged by the Investigator to have stabilized.
Section 6.3.2	All liver decompensation events included in the composite efficacy endpoint (Section 1.9.2) will be adjudicated by the Clinical Events Committee (CEC; see Section 6.5), as well as all DILI events (see Section 6.5). **Criteria used for reporting a potential DILI for adjudication are given below and correspond to the criteria leading to permanent study drug discontinuation.** For DILI adjudication, assessment may be performed using as baseline either historical AST, ALT, total bilirubin, and INR results meeting the requirements of within 8 weeks to 6 months of planned randomization visit (V1), or, using lab results from SV1 and V1 that are at least 8 weeks apart.
Section 6.5	The CEC will conduct adjudication of all disease progression events included in the primary composite efficacy long-term endpoint (Section 1.9.2~~, except for histological cirrhosis~~), all DILI events, and all major cardiovascular events as defined in the CEC charter. The CEC assessment and adjudication will occur in a blinded, consistent, and unbiased manner throughout the course of a study to determine whether the endpoints meet the protocol-specified criteria. The CEC will be comprised of 2 hepatologists, 2 cardiologists, ~~and~~ 1 endocrinologist **and 3 histopathologists**, all of whom will be independent of the participants in the study.
Section 8.1.2	**8.1.2 Adverse events of special interest (AESIs)** **AESIs are treatment emergent AEs corresponding to the conceptual definition of:** • **CPK elevations of severe intensity or leading to permanent study drug discontinuation** • **Muscle injury symptoms of severe intensity corresponding to:**

	○ **Muscle pain or Myalgia** ○ **Muscle spasms or Tremor** ○ **Muscle weakness** • **Transaminases elevations from baseline of severe intensity or leading to permanent study drug discontinuation** • **Liver injury events of severe intensity corresponding to:** ○ **Hepatic impairment** ○ **Hepatic failure** • **Gastrointestinal symptoms of severe intensity corresponding to:** ○ **Abdominal pain** ○ **Constipation** ○ **Diarrhea** ○ **Nausea** ○ **Vomiting** ○ **Acute cholecystis** ○ **Acute pancreatitis** • **Fatigue and Asthenia of severe intensity** • **Serum creatinine elevations of severe intensity or leading to permanent study drug discontinuation** • **Renal injury events of moderate or severe intensity corresponding to:** ○ **Renal failure** ○ **Renal impairment** ○ **Renal colic** **Treatment emergent Pregnancy and outcomes of Pregnancy will be considered as AESIs, and are described in the section 8.6.1.**
Section 8.3.2	8.3.2 Reporting a serious adverse event **or an adverse event of special interest** Serious AE reporting begins from signature of the patient ICF and ends at study end for each patient. **AESI reporting starts from first study drug intake and ends at study end for each patient.** Any SAE **or AESI** that is brought to the attention of the Investigator at any time after the reporting period and which is considered by him/her to be caused by the study drug within a reasonable possibility, should be reported. Any of the portal hypertension/cirrhosis related events described in Section 2.1.2 that are identified as potential primary efficacy endpoints for long-term evaluation will NOT be reported as SAEs unless it is determined by the adjudication committee that the event

does not meet the predefined criteria for an endpoint. Events that are identified as potential primary efficacy endpoints for long-term evaluation that are not confirmed by adjudication will be reported as described with the start of the reporting time window being the time of negative adjudication decision.

Investigators must notify, by ~~fax or~~ e-mail **or fax**, the Sponsor designated representative [redacted] of all SAEs **or AESIs-** IMMEDIATELY (within 24 hours of the Investigator becoming aware of the event).

ANY SERIOUS ADVERSE EVENTS, **OR ADVERSE EVENTS OF SPECIAL INTEREST,** WHETHER OR NOT RELATED TO THE STUDY DRUG, MUST BE REPORTED IMMEDIATELY (WITHIN 24 HOURS) TO [redacted] AT THE FOLLOWING FAX NUMBERS:

FAX numbers: [redacted]

Contact Person: [redacted]

Email: [redacted]

All SAEs **or AESIs** independent of the circumstances or suspected cause must be reported in ENGLISH on a SAE Form. The SAE**/AESI** Form should include a clearly written narrative describing signs, symptoms, **intensity** and treatment of the event, diagnostic procedures, as well as any relevant laboratory data and any sequelae, in order to allow a complete medical assessment of the case and independent determination of the possible causality.

The Investigator is also required to submit follow-up SAE**/AESI** reports to [redacted] within 24 hours of becoming aware of additional information such as diagnosis, outcome, causality assessment, results of specific investigations, and any new significant information that has not been previously reported.

It is critical that the information provided on the initial or follow-up SAE**/AESI** Form matches the information recorded in the source documents and the eCRF for the same event.
Copies of additional laboratory tests, consultation reports, postmortem reports, hospital case reports, autopsy reports, and other

	documents should be sent when requested and applicable. All provided reports must be anonymized. Follow-up reports relative to the patient's subsequent course must be submitted to [redacted] until the event has subsided or, in case of permanent impairment, until the condition stabilizes. The Sponsor or its designated representative will report all the relevant safety information to the concerned Competent Authorities and to the Independent Ethics Committee(s) (IRB/IEC) ~~concerned~~ according to the country-specific requirements. Investigator must fulfill his/her regulatory obligations to the Regulatory Authorities and/or to the Ethics Committee in accordance with local regulations. Depending on local regulations in different regions and countries, the Sponsor or designated clinical research organization (CRO) may be required to expedite report to the Regulatory Authorities for: • SAEs (including events related to study procedures) • SADRs **(a serious ADR)** • **SUSARs (**Suspected unexpected serious adverse reactions**)** ~~(SUSARs)~~
Section 8.3.3	The patient must be followed up until clinical recovery is complete and laboratory results have returned to normal, or until progression has been stabilized. This may imply that follow-up will continue after the patient has left the study **(i.e. after EoT visit), notably for the potential related adverse events,** and that additional investigations may be requested by the Sponsor. This information should be documented in the patient's medical records.
Section 8.5	Laboratory abnormalities are not necessarily recorded as AEs or SAEs. However, laboratory abnormalities that are considered clinically relevant by the Investigator must be recorded as an AE**, AESI** or SAE as applicable.
Section 8.6.1	~~The pregnancy itself is not considered an AE.~~
Section 9.2.2	The long term endpoint of clinical outcomes is a composite endpoint composed of death due to any cause, histological liver cirrhosis, and the full list of portal hypertension/cirrhosis related events:

	• Liver transplantation
	• MELD score ≥15 **for patients with baseline MELD score ≤12**
	• ~~HCC~~
	• the onset of:
	  ○ variceal bleed **requiring hospitalization,**
	  ○ hepatic encephalopathy **defined as West Haven/Conn score ≥2 and requiring hospitalization,**
	  ○ spontaneous bacterial peritonitis**,**
	  ○ ascites **requiring treatment.**
	  ○ ~~hepatorenal syndrome~~
	  ○ ~~hepatopulmonary syndrome~~
	  ○ ~~chronic gastrointestinal blood loss due to portal hypertensive gastropathy (provided that these lead to hospitalization or transfusion).~~

Section 9.4.2	The main analysis will be based on the ITT. Supportive analysis will be based on the ~~EES and~~ PPS.
Section 9.8	Safety data (exposure, AEs, **AESIs,** clinical laboratory tests, vital signs, and ECGs) will **be** summarized by treatment group using descriptive statistics. The main summaries of safety will be based on the SS. Additional safety analysis will be based on the FSS and the exploratory F1 cohort. Adverse events will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA). An overall summary of AEs will be provided. The number and percentage of patients reporting AEs will also be presented by MedDRA System Organ Class and preferred term. The AEs will be summarized by worst severity and relationship to study drug. **AESIs,** serious AEs, and AEs leading to discontinuation will also be summarized. Narratives will be added for all SAEs **and AESIs**.
Section 10.1	All study required patient data generated during the study will be recorded in the eCRF, with the exception of SAE**/AESI** forms and SF-36 which will be collected via ePRO (which is then transferred to the electronic data capture).
Section 11.1	Before enrolling any patients in this study, the Study Monitor will review the protocol, the brochure for clinical investigators, the eCRFs and instructions for their completion and return, the procedure for obtaining informed consent, and the procedure for reporting AEs and SAEs**/AESIs** with the Investigator.

Section 12.5	End of the research corresponds to the ~~end of participation (end of study EOT Visit) of~~ **last observation for** the last patient participating in the research.

Summary of minor changes to the protocol:

The following minor changes were made to the protocol. The changes do not impact the reliability of the data generated in the clinical trial or the safety or rights of the subjects:

- AESI has been added to the List of Abbreviations.
- The version number and date were updated throughout the protocol.
- Relevant sections of the synopsis were updated to keep consistency with the protocol.
- Study contact details for central laboratory have been updated.

CLINICAL TRIAL SYNOPSIS

Sponsor: GENFIT	Study Drug: Elafibranor (GFT505): Propanoic acid, 2- [2,6-dimethyl-4-[3-[4-(methylthio)phenyl]- 3-oxo-1(E)-propenyl] phenoxy]-2- methylpropanoic acid	Protocol Number: GFT505-315-1

Title of the study:
A Multicenter, Randomized, Double-Blind, Placebo-Controlled Phase III Study to Evaluate the Efficacy and Safety of Elafibranor in Patients with Nonalcoholic Steatohepatitis (NASH) and fibrosis

Phase:
Phase III

Indication:
NASH

Study design and dose levels:
Randomized, double-blind, parallel groups (placebo or elafibranor [GFT505]) placebo-controlled study, evaluating the efficacy and safety of elafibranor 120 mg QD versus placebo in an adult NASH population with fibrosis. The first double-blind 72-week treatment period will assess the efficacy and safety of elafibranor on the resolution of NASH without worsening of fibrosis at the surrogate endpoint efficacy analysis, followed by a Long-term Treatment Period (LTTP) to assess efficacy on progression to cirrhosis, all-cause mortality, and liver-related clinical outcomes as measured by the onset of any of the listed adjudicated events.

Dose level
120 mg

Route of administration:
Oral (1 tablet once daily [QD])

To assess the efficacy and safety of elafibranor as compared to placebo in adult NASH patients with fibrosis stage 2 or 3 (F2-F3), the primary and secondary objectives are as follows:

Primary objective – surrogate endpoint analysis
To evaluate the efficacy of elafibranor 120 mg QD for 72 weeks versus placebo on resolution of NASH without worsening of fibrosis.

- Resolution of NASH is defined as the disappearance of ballooning and disappearance or persistence of minimal lobular inflammation (grade 0 or 1) with an overall pattern of injury not qualifying for steatohepatitis.
- Worsening of fibrosis is evaluated using the NASH Clinical Research Network (CRN) fibrosis staging system and defined as progression of at least 1 stage.

Primary objectives – long-term endpoints
To evaluate the efficacy of elafibranor 120 mg QD versus placebo on clinical outcomes described as a composite endpoint composed of death due to any cause, histological liver cirrhosis, and the full list of portal hypertension/cirrhosis related events:

- Liver transplantation
- MELD score ≥15 for patients with a baseline MELD score ≤12
- the onset of:
  - variceal bleed requiring hospitalization,
  - hepatic encephalopathy defined as West Haven/Conn score ≥2 and requiring hospitalization,
  - spontaneous bacterial peritonitis,
  - ascites requiring treatment.

Key secondary objectives (at surrogate endpoint analysis)
To assess histological changes after 72 weeks of treatment on the following endpoint:

- Percentage of patients with improvement of fibrosis of at least 1 stage according to NASH CRN scoring.

To assess the clinical benefit after 72 weeks of treatment on the following metabolic endpoints:

- Changes from baseline in triglycerides, Non-HDL cholesterol, HDL cholesterol, LDL cholesterol, HbA1c (in diabetic patients), HOMA-IR (in non-diabetic patients)

Other secondary objectives

- To assess histological changes after 72 weeks of treatment and at the end of the LTTP on the following endpoints:
    - percentage of patients with resolution of NASH without worsening of fibrosis (at the end of LTTP)
    - percentage of patients with improvement of fibrosis of at least 1 stage according to NASH CRN scoring (at the end of LTTP)
    - percentage of patients with improvement of fibrosis of at least 1 stage according to NASH CRN scoring without worsening of NASH
    - percentage of patients with no worsening of Fibrosis and no worsening of NASH
    - percentage of patients with resolution of NASH and improvement of Fibrosis
    - percentage of patients with at least a 1 point improvement in histological scores (NASH CRN scoring: NAS [sum of steatosis, hepatic ballooning and lobular inflammation], steatosis, hepatic ballooning, lobular inflammation), fibrosis (NAFLD Ishak scoring system), or portal inflammation
    - percentage of patients with improvement of NAS of at least 2 points
    - percentage of patients with improvement of NAS of at least 2 points and with at least 1 point improvement in hepatic ballooning
    - percentage of patients with at least a 1 point improvement in disease activity score (sum of ballooning and lobular inflammation scores) according to NAS scoring and steatosis-activity- fibrosis (SAF) scoring
    - percentage of patients with at least a 1 point improvement in disease activity score (sum of ballooning and lobular inflammation scores) according to NAS scoring and with at least 1 point improvement in hepatic ballooning
    - percentage of patients with at least a 1 point improvement in disease activity score (sum of ballooning and lobular inflammation scores) according to steatosis-activity-fibrosis (SAF) scoring and with at least 1 point improvement in hepatic ballooning
    - percentage of patients with at least 2 points improvement in disease activity score according to NAS scoring and SAF scoring
    - changes in NAS, fibrosis (using NASH CRN and NAFLD Ishak scoring system), steatosis, hepatic ballooning, lobular inflammation, portal inflammation and SAF activity score
    - changes in area of fibrosis (normalized Collagen Proportional area in %) by morphometry
- To assess the following endpoints at Week 72, and at the end of the LTTP:
    - changes in liver enzymes and liver markers
    - changes in noninvasive markers of fibrosis and steatosis
    - changes in lipid parameters
    - variation in body weight
    - changes in insulin resistance and glucose homeostasis markers
    - changes in inflammatory markers
    - changes in cardiovascular risk profile as assessed by Framingham scores
    - changes in liver stiffness by Fibroscan measurement
    - changes in quality of life (36-Item Short-Form Health Survey [SF-36] questionnaire)
- To assess the onset to:
    - histological liver cirrhosis
    - death of any cause
    - any portal hypertension or cirrhosis related events
    - cardiovascular events
    - liver-related death events.

Exploratory objectives

- To constitute a biobank for discovery and validation of biomarkers in NASH.

Exploratory objectives for F1 group and the overall population (whatever the fibrosis stage – F1, F2 or F3)

- To explore, in F1 patients and in the overall population whatever the fibrosis stage (F1, F2 or F3), the same endpoints as for the primary and secondary objectives

Safety secondary objectives

- To assess the tolerability and safety of once a day administration of oral doses of elafibranor 120 mg:
  - serious adverse events, adverse events, adverse events of special interest, physical examination, vital signs, medical history, electrocardiogram
  - hematological parameters
  - liver markers
  - renal biomarkers (including urinalysis)
  - cardiac biomarkers
  - metabolic parameters
  - other biochemical safety markers.

Patient population:

NASH diagnosed as:

Steatohepatitis evaluated by a centrally-read liver biopsy taken within 6 months prior to Screening (if no historical biopsy is available for NASH diagnosis, a liver biopsy will be performed during the Screening Period) with:

- At least a score of 1 in each component of the NAS (steatosis scored 0-3, ballooning degeneration scored 0-2, and lobular inflammation scored 0-3).
- NAS ≥4.
- fibrosis stage of 1 or greater and below 4, according to the NASH CRN fibrosis staging system. For patients with fibrosis stage 1, only patients at high risk of progression will be included, meaning with a NAS ≥5 and at least 2 of the following conditions: persistent elevated alanine aminotransferase (ALT; absence of normal value of ALT within the past year), obesity defined by a body mass index (BMI) ≥30, metabolic syndrome (NCEP ATP III definition), type 2 diabetes, or homeostasis model assessment of insulin resistance (HOMA-IR) >6.

At the end of the 72-week treatment period, patients will continue in the double-blind LTTP. Patients will be monitored by notably measuring the potential appearance of cirrhosis (based on FibroScan measurement for presence of cirrhosis associated with biological and clinical assessments). If histological cirrhosis is confirmed as well as any other event listed in the long-term composite endpoint, patients will be discontinued from study.

Number of estimated randomized F2-F3 Patients: at least 2022 patients (ratio 2:1)

- 674 patients in placebo group
- 1348 patients in elafibranor (GFT505) group

An additional 202 (10% of the F2-F3 patients) F1 patients at high risk of progression will be included as an exploratory arm.

Number of participating centers (planned): ~270 centers

Number of participating countries: 24 (Belgium, France, Germany, Italy, the Netherlands, Romania, Spain, UK, Switzerland, Portugal, Denmark, Finland, Sweden, Czech Republic, Russia, Turkey, USA, Canada, Mexico, Colombia, Argentina, Chile, Australia, South Africa)

Study duration per patient:

Estimated duration approximately 96 months, based on 456 patients experiencing a long-term composite endpoint event.

Schedule:

- Screening Period: Week -12 to Week -1 prior to Randomization.
- First Treatment Period: Week 0 to Week 72: period of treatment with elafibranor (GFT505) or placebo for 72 weeks.
- Long-term Treatment Period: Week 72 to end of study: extension of treatment with elafibranor (GFT505) or placebo (until occurrence of prespecified number of events).

Inclusion criteria:

Patients must meet all of the following inclusion criteria to be eligible for enrollment in the trial:

1. Males or females aged from 18 to 75 years inclusive at first Screening Visit.
2. Must provide signed written informed consent and agree to comply with the study protocol.
3. Females participating in this study must be of nonchildbearing potential or using highly efficient contraception for the full duration of the study and for 1 month after the end of treatment, as described below:
   - Cessation of menses for at least 12 months due to ovarian failure,

- Surgical sterilization such as bilateral oopherectomy, hysterectomy, or medically documented ovarian failure
- If requested by local IRB regulations and/or National laws, sexual abstinence may be considered adequate (the reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient)
- Using a highly effective nonhormonal method of contraception (bilateral tubal occlusion, vasectomized partner, or intra-uterine device)
- Double contraception with barrier AND highly effective hormonal method of contraception (oral, intravaginal, or transdermal combined estrogen and progestogen hormonal contraception associated with inhibition of ovulation; oral, injectable, or implantable progestogen-only hormonal contraception associated with inhibition of ovulation; or intrauterine hormone-releasing system). The hormonal contraception must be started at least 1 month prior to Randomization.

4. Histological confirmation of steatohepatitis on a diagnostic liver biopsy by central reading of the slides (biopsy obtained within 6 months prior to Screening or during the Screening Period) with at least 1 in each component of the NAS (steatosis scored 0-3, ballooning degeneration scored 0-2, and lobular inflammation scored 0-3).
5. NAS ≥4.
6. Fibrosis stage of 1 or greater and below 4, according to the NASH CRN fibrosis staging system. For patients with fibrosis stage 1, only patients at high risk of progression will be included meaning with a NAS ≥5 and at least 2 of the following conditions: persistent elevated ALT (absence of normal value of ALT within the past year), obesity defined by a BMI ≥30, metabolic syndrome (NCEP ATP III definition), type 2 diabetes, or HOMA-IR >6.
7. Patients in whom it is safe and practical to proceed with a liver biopsy, and who agree to have:
   - 1 liver biopsy during the Screening Period for diagnostic purpose (if no historical biopsy within 6 months before Screening is available)
   - 1 liver biopsy after 72-weeks of treatment for assessment of the treatment effects on NASH
   - a final liver biopsy after approximately 4 years of treatment (V13), unless a liver biopsy has already been performed within the past year
   - 1 liver biopsy performed only in the case of suspicion of cirrhosis (to have a histological confirmation).
8. If a patient is treated with 1 of the following drugs: vitamin E (>400 IU/day), polyunsaturated fatty acids (>2 g/day), or ursodeoxycholic acid; a stable dose from at least 6 months prior to diagnostic liver biopsy is required.
9. For patients with type 2 diabetes, glycemia must be controlled. If glycemia is controlled by antidiabetic drugs, change in anti-diabetic therapy must follow these requirements:
   - no qualitative change 6 months prior to diagnostic liver biopsy up to Randomization (i.e., implementation of a new anti-diabetic therapy) for patients treated with metformin, gliptins, sulfonylureas, sodium/glucose cotransporter (SGLT) 2 inhibitors, glucagon-like peptide (GLP)- 1 agonists, or insulin. Dose changes of these medications are allowed in the 6 months prior to diagnostic liver biopsy, except for GLP-1 agonists, which must remain on stable dose in the 6 months prior to diagnostic liver biopsy.
   - no implementation of GLP-1 agonists and SGLT2 inhibitors up to 72 weeks of treatment (V7).

   Initiation of any other antidiabetic drugs is allowed after Randomization based on treating physicians' judgment, except for glitazones which are prohibited 6 months prior to diagnostic liver biopsy until the end of treatment.

Exclusion criteria:

Patients who meet any of the following criteria will be excluded from entering the study:

1. Known chronic heart failure (Grade I to IV of New York Heart Association classification).
2. History of efficient bariatric surgery within 5 years prior to Screening, or planned bariatric surgery in the course of the study.
3. Uncontrolled hypertension during the Screening Period despite optimal antihypertensive therapy.
4. Type 1 diabetes patients.
5. Patients with hemoglobin A1c [HbA1c] >9.0%. If abnormal at the first Screening Visit, the HbA1c measurement can be repeated at the latest 2 weeks prior to Randomization. A repeated

abnormal HbA1c (HbA1c >9.0%) leads to exclusion.

6. Patients receiving thiazoledinediones (glitazones [pioglitazone, rosiglitazone]) unless the drug was discontinued at least 6 months before the diagnostic liver biopsy.
7. Patients with a history of clinically significant acute cardiac event within 6 months prior to Screening such as: stroke, transient ischemic attack, or coronary heart disease (angina pectoris, myocardial infarction, revascularization procedures).
8. Weight loss of more than 5% within 6 months prior to Randomization.
9. Compensated and decompensated cirrhosis (clinical and/or histological evidence of cirrhosis). Notably, NASH patients with fibrosis stage = 4 according to the NASH CRN fibrosis staging system are excluded.
10. Current or recent history (<5 years) of significant alcohol consumption. For men, significant consumption is typically defined as higher than 30 g pure alcohol per day. For women, it is typically defined as higher than 20 g pure alcohol per day.
11. Pregnant or lactating females or females planning to become pregnant during the study period.
12. Other well documented causes of chronic liver disease according to standard diagnostic procedures including, but not restricted to:
    - positive hepatitis B surface antigen
    - positive hepatitis C Virus (HCV) RNA (tested for in case of known cured HCV infection or positive HCV Ab at Screening)
    - suspicion of drug-induced liver disease
    - alcoholic liver disease
    - autoimmune hepatitis
    - Wilson's disease
    - primary biliary cirrhosis, primary sclerosing cholangitis
    - genetic homozygous hemochromatosis
    - known or suspected hepatocellular carcinoma (HCC)
    - history or planned liver transplant, or current MELD score >12
13. Where applicable, patients not covered by Health Insurance System and/or not in compliance with the recommendations of National Law in force applicable to clinical trials.
14. Patients who cannot be contacted in case of emergency.
15. Known hypersensitivity to the investigation product or any of its formulation excipients.
16. Patients with previous exposure to elafibranor.
17. Patients who are currently participating in, plan to participate in, or have participated in an investigational drug trial or medical device trial containing active substance within 30 days or five half-lives, whichever is longer, prior to Screening.

Concomitant medications:

18. Fibrates are not permitted from 2 months before Randomization. Patients that used statins, ezetimibe, or other nonfibrate lipid lowering drugs before Screening may participate if the dosage has been kept constant for at least 2 months prior to Screening.
19. Currently taking drugs that can induce steatosis/steatohepatitis including, but not restricted to: corticosteroids (parenteral & oral chronic administration only), amiodarone (Cordarone), tamoxifen (Nolvadex), and methotrexate (Rheumatrex, Trexall), which are not permitted 30 days prior to Screening and up to end of treatment.
20. Currently taking any medication that could interfere with study medication absorption, distribution, metabolism, or excretion or could lead to induction or inhibition of microsomal enzymes, e.g., indomethacin, which are not permitted from Randomization until end of treatment.

Associated illnesses or conditions:

21. Any medical conditions that may diminish life expectancy to less than 2 years including known cancers.
22. Evidence of any other unstable or, untreated clinically significant immunological, endocrine, hematological, gastrointestinal, neurological, neoplastic, or psychiatric disease
23. Mental instability or incompetence, such that the validity of informed consent or ability to be compliant with the study is uncertain.

In addition to the above criteria, patient should not present any of the following biological exclusion criteria:

24. Positive anti-human immunodeficiency virus antibody.

25. Aspartate aminotransferase (AST) and/or ALT >10 x upper limit of normal (ULN).
26. Conjugated bilirubin > 1.50mg/dL due to altered hepatic function **Note**: Gilbert Disease patients are allowed into the study.
27. International normalized ratio >1.40 due to altered hepatic function.
28. Platelet count <100,000/mm^3 due to portal hypertension.
29. Serum creatinine levels >1.53 mg/dL in males and >1.24 mg/dL in females.
30. Significant renal disease, including nephritic syndrome, chronic kidney disease (defined as patients with markers of kidney damage or estimated glomerular filtration rate [eGFR] of less than 60 ml/min/1.73 m^2).
31. Unexplained serum creatine phosphokinase (CPK) >3 x the ULN. In case of explained elevated CPK >3 x the ULN, the measurement can be repeated prior to Randomization. In this case, retest should be performed within 1 to 2 weeks after initial test. A CPK retest >3 x ULN leads to exclusion.

Criteria for Evaluation:

Primary endpoint

Surrogate endpoint - resolution of NASH (at surrogate endpoint analysis)

To evaluate the efficacy of elafibranor 120 mg versus placebo on the resolution of NASH without worsening of fibrosis after 72 weeks of treatment.

Long-term endpoint – clinical outcomes (at final analysis)

To evaluate the efficacy of elafibranor 120 mg QD versus placebo on clinical outcomes described as a composite endpoint composed of death due to any cause, histological liver cirrhosis, and the full list of portal hypertension/cirrhosis related events:

- liver transplantation
- MELD score ≥15 for patients with a baseline MELD score ≤12
- the onset of:
    - variceal bleed requiring hospitalization,
    - hepatic encephalopathy defined as West Haven/Conn score ≥2 and requiring hospitalization,
    - spontaneous bacterial peritonitis,
    - ascites requiring treatment.

The final analysis will be performed when 456 patients experience an event listed above. This is expected to occur approximately 96 months after the first patient is randomized.

Key secondary endpoints (at surrogate endpoint analysis)

Percentage of patients with improvement of fibrosis of at least 1 stage according to NASH CRN scoring at 72 weeks.

Changes from baseline to Week 72 in triglycerides, Non-HDL cholesterol, HDL cholesterol, LDL cholesterol, HbA1c (in diabetic patients), HOMA-IR (in non-diabetic patients)

Other secondary endpoints

- To assess histological changes after 72 weeks of treatment and at the end of the LTTP on the following endpoints:
    - percentage of patients with resolution of NASH without worsening of fibrosis (at the end of LTTP)
    - percentage of patients with improvement of fibrosis of at least 1 stage according to NASH CRN scoring (at the end of LTTP)
    - percentage of patients with improvement of fibrosis of at least 1 stage according to NASH CRN scoring without worsening of NASH
    - percentage of patients with no worsening of fibrosis and no worsening of NASH
    - percentage of patients with resolution of NASH and improvement of Fibrosis
    - percentage of patients with at least a 1 point improvement in histological scores (NASH CRN scoring: NAS [sum of steatosis, hepatic ballooning and lobular inflammation], steatosis, hepatic ballooning, lobular inflammation), fibrosis (NAFLD Ishak scoring system), or portal inflammation
    - percentage of patients with improvement of NAS of at least 2 points
    - percentage of patients with improvement of NAS of at least 2 points and with at least 1 point improvement in hepatic ballooning
    - percentage of patients with at least a 1 point improvement in disease activity score

(sum of ballooning and lobular inflammation scores) according to NAS scoring and steatosis-activity-fibrosis (SAF) scoring
    - percentage of patients with at least a 1 point improvement in disease activity score (sum of ballooning and lobular inflammation scores) according to NAS scoring and with at least 1 point improvement in hepatic ballooning
    - percentage of patients with at least a 1 point improvement in disease activity score (sum of ballooning and lobular inflammation scores) according to steatosis-activity-fibrosis (SAF) scoring and with at least 1 point improvement in hepatic ballooning
    - percentage of patients with at least 2 points improvement in disease activity score according to NAS scoring and SAF scoring
    - changes in NAS, fibrosis (using NASH CRN and NAFLD Ishak scoring system), steatosis, hepatic ballooning, lobular inflammation, portal inflammation, SAF activity score
    - changes in area of fibrosis (normalized Collagen Proportional area in %) by morphometry.
- To assess the following endpoints at Week 72, and at the end of the LTTP:
    - changes in liver enzymes and liver markers
    - changes in noninvasive markers of fibrosis and steatosis
    - changes in lipid parameters
    - variation in body weight
    - changes in insulin resistance and glucose homeostasis markers
    - changes in inflammatory markers
    - changes in cardiovascular risk profile as assessed by Framingham scores
    - changes in liver stiffness by Fibroscan measurement
    - changes in quality of life (SF-36 questionnaire).
- To assess the onset of:
    - histological liver cirrhosis
    - death of any cause
    - any portal hypertension or cirrhosis related events
    - cardiovascular events
    - liver-related death events.

Exploratory endpoints

- To constitute a biobank for discovery and validation of biomarkers in NASH.

Study Duration (planned): estimated 96 months (First Patient First Visit [FPFV]-Last patient last visit [LPLV])

- Regulatory/ethics committee submission: January 2016
- Initiation visits: March 2016 – Sep 2018
- Recruitment period: March 2016 – May 2020
- FPFV: March 2016
- Surrogate endpoint analysis: Q1 2020 – Q2 2020
- LPLV (LTTP): estimated within Q1 2024

Data Safety Monitoring Board (DSMB)

An independent DSMB will be established in order to review the progress of the study and to perform a safety data review on a regular basis during the trial to protect patient welfare and preserve study integrity. The DSMB will also review the interim analysis results and provide final recommendations regarding trial termination due to futility and adjustment of the target number of primary events.
The DSMB will consist of at least 5 experienced physicians (1 endocrinologist, cardiologist, hepatologist, oncologist, and nephrologist) and 1 statistician, all of whom will be independent of the participants in the study. The DSMB Charter will define the role, responsibilities, rules, and tasks of the DSMB.

Clinical events committee (CEC)

The CEC will conduct the adjudication of all disease progression events included in the primary composite efficacy long-term endpoint, all drug-induced liver injury events, and all major cardiovascular events as defined in the CEC charter. The CEC assessment and adjudication will occur in a blinded, consistent, and unbiased manner throughout the course of a study to determine whether the endpoints meet the protocol-specified criteria.
The CEC will be comprised of 2 hepatologists, 2 cardiologists, 1 endocrinologist, and 3 histopathologists all of whom will be independent of the participants in the study.

Table 1: STUDY GENERAL ASSESSMENT SCHEDULE

	Screening Period			First Treatment Period							Long-term Treatment Period		End Of Study Treatment
Visit	**SV1**[4]	**SV2**[4]	**SPV**[5]	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**Phone Visit PV1-PVn**	**V8-Vn**	**EOT**[13]
Week	*-12 to -1*		*-1*[5]	*0*[6]	*12*[6]	*24*[6]	*36*[6]	*48*[6]	*60*[6]	*72*[6]	*(every 24 weeks starting 12 weeks after V7)*[8]	*(every 24 weeks starting after V7)*[9]	*30 days after final study drug administration*
Permitted Margin				**0**	**±1 week after V1**	**± 1 week after V1**	**± 1 week after V1**	**± 1 week after V1**	**± 1 week after V1**	**± 1 week after V1**	**± 2 weeks Compared to V7**	**± 2 weeks Compared to V7**	**± 1 week after last administration**
Obtain informed consent	X												
Medical history / demographics	X												
Check inclusion / exclusion criteria	X			X[7]									
Adequate diet and lifestyle recommendations, including alcohol restrictions and smoking habits	X												
Confirmation of diet and lifestyle compliance, including alcohol restrictions and smoking habits				X	X	X	X	X	X	X	X	X	X
Physical examination	X			X	X	X	X	X	X	X		X	X
Vital signs & height[1] **& weight measurement**	X			X	X	X	X	X	X	X		X	X
Waist circumference	X			X		X		X		X		X	X

	Screening Period			First Treatment Period							Long-term Treatment Period		End Of Study Treatment
Visit	**SV1**[4]	**SV2**[4]	**SPV**[5]	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**Phone Visit PV1-PVn**	**V8-Vn**	**EOT**[13]
Week	*-12 to -1*		*-1*[5]	*0*[6]	*12*[6]	*24*[6]	*36*[6]	*48*[6]	*60*[6]	*72*[6]	*(every 24 weeks starting 12 weeks after V7)*[8]	*(every 24 weeks starting after V7)*[9]	*30 days after final study drug administration*
Permitted Margin				0	±1 week after V1	± 1 week after V1	± 1 week after V1	± 1 week after V1	± 1 week after V1	± 1 week after V1	± 2 weeks Compared to V7	± 2 weeks Compared to V7	± 1 week after last administration
12-Lead ECG				X			X			X		X[10]	X
Lab evaluation (see Table 2)	X	X		X	X	X	X	X	X	X		X	X
Send sample for central histological evaluation of NASH diagnosis / change	X	X								X		X[11]	
Liver biopsy		X[4]								X		X[11]	
Phone call to patient to confirm eligibility of histology criteria			X[5]										
FibroScan[2]				X						X		X	
Contact the patient prior to visit[3]				X	X	X	X	X	X	X		X	X
Randomization				X									
IXRS registration	X			X	X	X	X	X	X	X	X	X	X
Review prior / concomitant medication	X			X	X	X	X	X	X	X	X	X	X

	Screening Period			First Treatment Period							Long-term Treatment Period		End Of Study Treatment
Visit	**SV1**[4]	**SV2**[4]	**SPV**[5]	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**Phone Visit PV1-PVn**	**V8-Vn**	**EOT**[13]
Week	*-12 to -1*		*-1*[5]	*0*[6]	*12*[6]	*24*[6]	*36*[6]	*48*[6]	*60*[6]	*72*[6]	*(every 24 weeks starting 12 weeks after V7)*[8]	*(every 24 weeks starting after V7)*[9]	*30 days after final study drug administration*
Permitted Margin				**0**	**±1 week after V1**	**± 1 week after V1**	**± 1 week after V1**	**± 1 week after V1**	**± 1 week after V1**	**± 1 week after V1**	**± 2 weeks Compared to V7**	**± 2 weeks Compared to V7**	**± 1 week after last administration**
Quality of life assessment				X		X		X		X		X[12]	X
Adverse events	X	X		X	X	X	X	X	X	X	X	X	X
Data collection on clinical outcomes					X	X	X	X	X	X	X	X	X
Study placebo or drug dispensation				X	X	X	X	X	X	X		X	
Drug accountability					X	X	X	X	X	X	X	X	X

Abbreviations: ECG = electrocardiogram; EOT = end of treatment; IXRS = Interactive voice/web Response System; LTTP = Long-term Treatment Period; NASH = nonalcoholic steatohepatitis; PV = phone visit; QOL = quality of life; SV = Screening visit; V = visit

1. Height is measured only at visit SV1.
2. Where possible FibroScan must be done at the day of visit. Otherwise, it can be performed within 7 days around the visit date.
3. During the study, the patient should be contacted at least 1 week before the next visit as a reminder on procedures and IP return.
4. The visits to be performed during the screening period should be scheduled according to the following requirements:
   - If there are historical lab values for AST, ALT, total bilirubin and INR that are within 8 weeks to 6 months of the planned Randomization visit (V1) these results can be used as the first baseline values in case of DILI adjudication. If there are no historical lab values that meet this requirement, then SV1 and V1 must be scheduled at least 8 weeks apart.
   - The visit SV2 only occurs if no historical biopsy within 6 months before the Screening Visit is available. A screening liver biopsy and slides shipment to the

central pathologist must be performed at least 4 weeks before Randomization, in order to obtain the results in time. However, in some exceptional cases, the central reading process can be expedited allowing a shorter time between SV1 or SV2 and V1. Coagulation (platelet count and PT [INR]) should be checked locally prior to this liver biopsy (according to local medical standards in each hospital).

- Randomization visit can be scheduled as soon as all the results are available to confirm the eligibility of the patients

5. Screening Phone Visit. Telephone contact for all patients at least 1 week before V1. Patients should be contacted regarding eligibility confirmation within 1 week prior to Randomization Visit V1. In case of ineligibility, the patient should be contacted as soon as possible.
6. The maximum time period between visits in the First Treatment Period is to be 96 days due to the study drug supply provided to the patient.
7. Check of all inclusion/exclusion criteria, including biological and histological criteria assessed at SV1 and SV2.
8. Phone visits every 24 weeks starting 12 weeks after V7 for safety, data collection on clinical outcomes, and IP compliance control. If any information during this phone contact requires a visit, the Investigator may decide to perform an unscheduled visit. Phone visits may also be performed at the same frequency for the follow-up of patients having permanently discontinued study drug but remaining in the study (Same information collected except IP compliance control).
9. The maximum time period between visits in the Long-term Treatment Period (LTTP) is to be 192 days due to the study drug supply provided to the patient.
10. In the LTTP the first ECG will be performed at V9 and then every 48.
11. Liver biopsy will be performed after approximately 4 years of treatment (V13) and in the case of suspicion of cirrhosis (based on FibroScan and/or clinical or biological assessment). In the case that the suspicion of cirrhosis is not confirmed by liver biopsy the patient shall remain on the study and a liver biopsy will be performed after approximately 4 years of treatment (V13, unless a biopsy has already been performed within the year). Blood sampling (coagulation tests; see Table 2) are to be performed locally before the biopsy.
12. QOL assessment questionnaire to be completed at 24 (V8), 48 (V9), and 96 (V11) weeks in the LTTP (following approximately 96, 120, and 168 weeks of treatment, respectively), and every 48 weeks thereafter.
13. EOT Visit to be performed 30 days after final study drug administration at the end of study or for any premature discontinuation (permanent study drug discontinuation or trial discontinuation).

Table 2: STUDY BIOLOGICAL ASSESSMENT SCHEDULE

Visit	Screening Period		First Treatment Period							Long-term Treatment Period	End of Study Treatment
	SV1 SB1[6]	SB2[7]	V1 B1	V2 B2	V3 B3	V4 B4	V5 B5	V6 B6	V7 B7	V8 to Vn B8 to Bn	EOT
Week	*-12 to -1*	*Prior to liver biopsy*	*0*	*12*	*24*	*36*	*48*	*60*	*72*	*Every 24 w eeks*	*30 days after final study drug administration*
Hematology *Hemoglobin, hematocrit, RBC, WBC, differential count, platelet count, reticulocytes count, and PT (INR)*	X		X	X	X	X	X	X	X	X	X
Coagulation - local lab testing prior to liver biopsy *Platelet count, PT (INR)* [1]		X							X	X [1]	
Serology *HIV ab I/II, HBsAg, and HCV Ab (positive HCV RNA in case HCV Ab >0 or known cured hepatitis C infection* [2]*)*	X										
Screening Visit 1 - chemistry panel *HbA1c* [2]*, fasting plasma glucose, insulin (fasting), HOMA-IR creatinine, eGFR, GGT, AST, ALT, CPK* [2]*, alkaline phosphatase, total and conjugated bilirubin, sodium, TG, and MELD score*	X										
V1 to Vn total chemistry panel *HbA1c, fasting plasma glucose, creatinine, eGFR, GGT, AST, ALT, CPK, alkaline phosphatase, total proteins, albumin, electrolytes (sodium, potassium, chloride, calcium), uric acid, urea (BUN), total and conjugated bilirubin, hsCRP, total cholesterol, nonHDL-C, HDL-C, TG, calculated VLDL-C, ApoAI, ApoB, calculated LDL-C, and MELD score*			X [6]	X	X	X	X	X	X	X	X

Visit	Screening Period		First Treatment Period							Long-term Treatment Period	End of Study Treatment
	SV1 SB1[6]	SB2[7]	V1 B1	V2 B2	V3 B3	V4 B4	V5 B5	V6 B6	V7 B7	V8 to Vn B8 to Bn	EOT
Week	*-12 to -1*	*Prior to liver biopsy*	*0*	*12*	*24*	*36*	*48*	*60*	*72*	*Every 24 w eeks*	*30 days after final study drug administration*
Urinalysis *albumin, creatinine, ACR, and microscopic analysis* *α1 microglobulin*, β-NAG,* N-Gal*, IL-18*, KIM-1*,*			X	X	X	X	X	X	X	X	X
Urinalysis (dipstick) *Specific gravity, pH, protein, glucose, ketones, bilirubin, urobilinogen, blood, nitrite, and leukocytes*	X		X	X	X	X	X	X	X	X	X
Urinary pregnancy tests [3]	X		X	X	X	X	X	X	X	X	X
Inflammatory markers *Fibrinogen, and haptoglobin*			X		X		X		X	X	X
Other Liver markers *CK18 (M65 & M30), adiponectin, ferritin, FGF19 & FGF21, alpha2 macroglobulin, hyaluronic acid, PIIINP, TIMP-1, and CHI3L1* [4]			* [4]		*		*		* [4]	* [4]	*
Calculated fibrosis & steatosis index *Fibrotest, ELF, NAFLD Fibrosis score, Steatotest, FLI, Fibrometre S, and FIB-4*			*		*		*		*	*	*
Other safety markers *Homocysteine, NT-ProBNP, troponin-T, and cystatin C*			*		*		*		*	*	*
Special glycemic and other lipid parameters *Insulin(fasting), HOMA-IR, Fructosamine, C-peptide, FFA, small dense LDL, ApoAII, Apo CIII, and Apo E*			*		*		*		*	*	*

Visit	Screening Period		First Treatment Period							Long-term Treatment Period	End of Study Treatment
	SV1 SB1[6]	SB2[7]	V1 B1	V2 B2	V3 B3	V4 B4	V5 B5	V6 B6	V7 B7	V8 to Vn B8 to Bn	EOT
Week	*-12 to -1*	*Prior to liver biopsy*	*0*	*12*	*24*	*36*	*48*	*60*	*72*	*Every 24 w eeks*	*30 days after final study drug administration*
Sampling for additional parameters *Whole blood [5], plasma, and serum bank*	* [5]		*	*	*	*	*	*	*	*	*

X = results available within 2 working days (routine analysis) * = batch analysis

Abbreviations Ab = antibody; ACR = albumin–creatinine ratio; Ag = antigen; ALT = alanine aminotransferase; Apo = apolipoprotein; AST = aspartate aminotransferase; β-NAG = N-acetyl-β-D- glucosaminidase; BUN = blood urea nitrogen; B = biological assessment Visit; CHI3L1 = chitinase-3-like protein 1; CK18 = cytokeratin 18; CPK = creatine phosphokinase; eGFR = estimated glomerular filtration rate; ELF = enhanced liver fibrosis; EOT = end of study treatment; FFA = free fatty acid; FGF = fibroblast growth factor; FIB-4 = fibrosis 4 score; FLI = fatty liver index; GGT = gamma-glutamyl transferase; HbA1c = hemoglobin A1c; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HDL-C = high density lipoprotein-C; HIV = human immunodeficiency virus; HOMA-IR = homeostasis model assessment of insulin resistance; hsCRP = high-sensitivity C-reactive protein; IL-18 = interleukin 18; INR = international normalized ratio; KIM-1 = kidney injury molecule-1; LDL-c = low density lipoprotein-C; MDRD = modification of diet in renal disease; MELD = model end stage liver disease; NAFLD = nonalcoholic fatty liver disease; N-Gal = neutrophil gelatinase-associated lipocalin; NT-ProBNP = N-terminal of the prohormone brain natriuretic peptide; PIIINP = type III procollagen peptide; PT = prothrombin time; TIMP-1 = tissue inhibitors of metalloproteinases 1; RBC = red blood cell; SB = Screening biological assessment Visit; SV = Screening Visit; TG = triglyceride; VLDL-C = very low density lipoprotein-C; V = Visit; WBC = white blood cell.

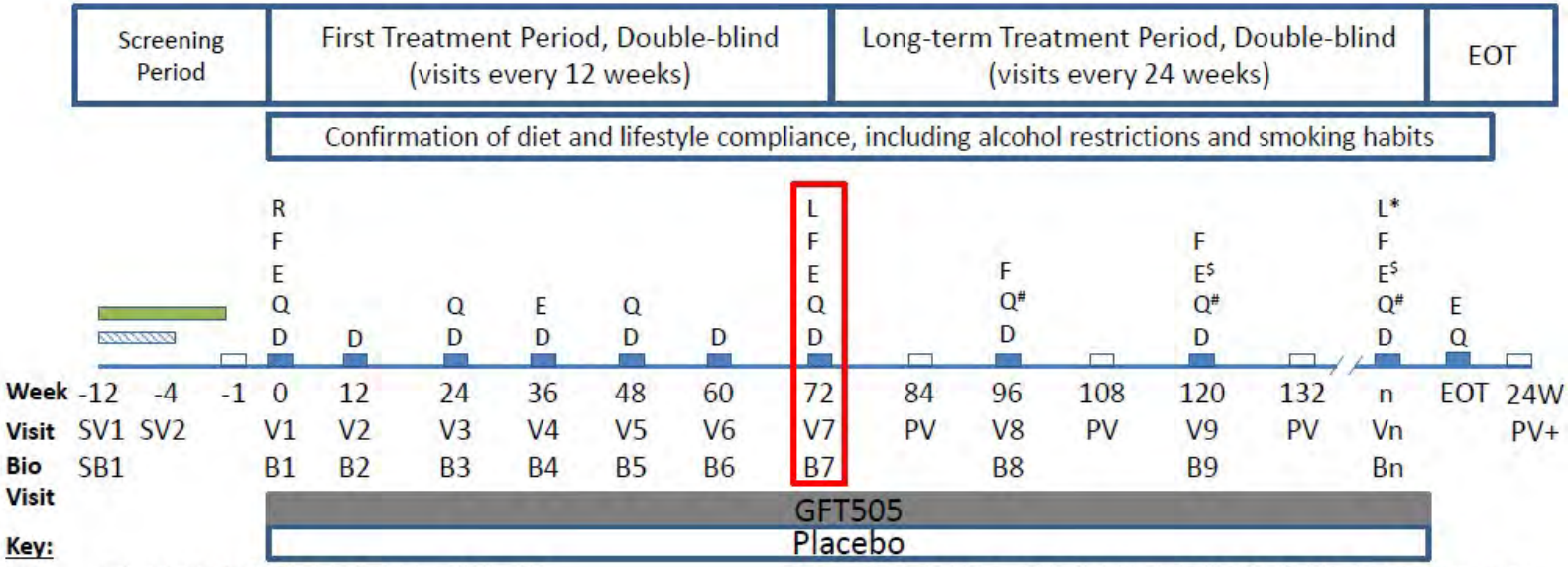
1. Coagulation (platelet count and PT [INR]) should be checked prior to any liver biopsy (according to local medical standards in each hospital). To be done through a local laboratory. Liver biopsy will be performed after 72 weeks (V7) and after approximately 4 years of treatment (V13) and in the case of suspicion of cirrhosis (based on FibroScan and/or clinical or biological assessment). In the case that the suspicion of cirrhosis is not confirmed by liver biopsy the patient shall remain on the study and a liver biopsy will be performed after approximately 4 years of treatment ([V13] unless a biopsy has already been performed within the past year).
2. Upon receipt of the results of the biological assessment performed at SV1, retesting or additional testing may be needed during the Screening Period:

- CPK can be repeated prior to Randomization (V1) within 1 to 2 weeks after initial test.
- HbA1c can be repeated prior to Randomization (V1), at the latest 2 weeks prior to planned Randomization.
- HCV RNA can be tested, at SV1 in case of known cured hepatitis c infection, or in case of positive HCV Ab at SV1, at a retest screening visit at the latest 2 weeks prior to the planned Randomization (V1).

3. Dipstick at site for WOCBP only. In addition, home pregnancy tests are to be performed by WOCBP every 4 weeks from V1 (see Table 1 and Figure 2).
4. CHI3L1 to be tested only at V1, V7, and at the time of 4 years biopsy (V13).

5. Whole blood sample will be only taken at SV1 while plasma and serum samples are to be taken at every visit ONLY for patients who have signed the pharmacogenomic and biomarker ICF.
6. If no historical values of AST, ALT, total bilirubin and INR meeting the requirements of within 8 weeks to 6 months of planned randomization visit (V1) are available, then SV1 and V1 must be scheduled at least 8 weeks apart in order to have 2 consecutive values for DILI adjudication. In any case, the visits should be scheduled in order to obtain the needed results prior to the randomization.
7. SB2, additional visit in the Screening Period if required for coagulation prior to liver biopsy

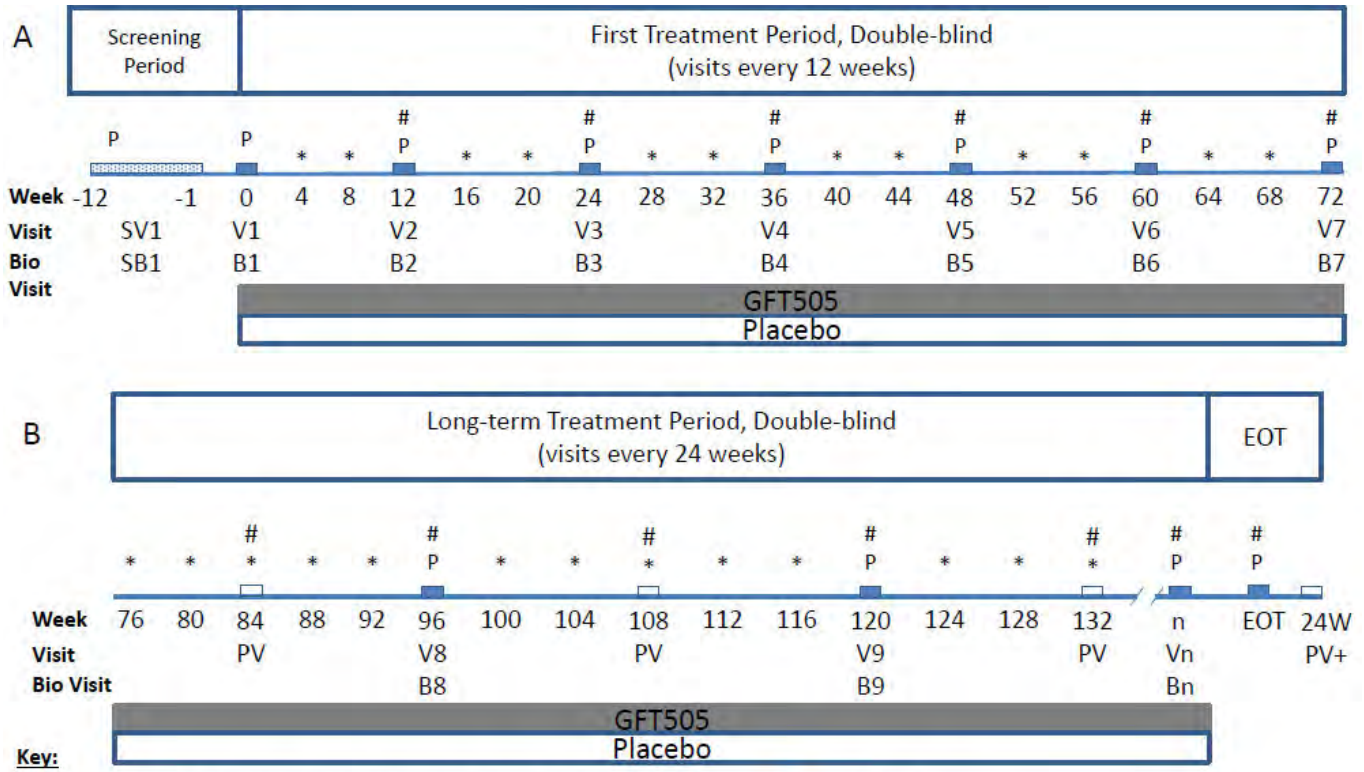
Figure 1: STUDY DURATION AND VISIT SCHEDULE



Key:

Bio Visit	Scheduled visits for biological assessment sampling	D	Study placebo or drug dispensation. No study placebo or drug dispensation will occur on the final Vn visit during the Long-term Treatment Period.
E	Electrocardiogram (ECG)	EOS	End of study
EOT	End of study treatment visit performed 30 days after final study drug administration at the end of study or for any premature discontinuation (permanent study drug discontinuation or trial discontinuation)	PV PV+	PV for safety, data collection of clinical outcomes, home pregnancy test results, and IP compliance control After EOT, patients without study outcome, can be followed up by phone visits every 24 weeks for safety and clinical outcomes up to the EOS.
L	Liver biopsy	F	FibroScan
Q	Quality of Life questionnaire	R	Randomization
S	Screening		Visit including clinical and laboratory evaluations
	Screening visit SV1 to occur between Weeks -12 and -1		Phone visit (for confirmation of eligibility in Week -1, for safety and drug accountability in Long-term Treatment Period, and for safety, diagnosis of cirrhosis and occurrence of clinical outcomes including liver and cardiovascular events for patients who have discontinued study drug for reasons other than an event in the primary composite endpoint for long-term efficacy [every 24 weeks after EOT])
	Screening visit SV2 to occur between Weeks -12 and -4		
#	Quality of life questionnaire in Long-term Treatment Period performed at Visits V8, V9, and V11, and every 48 weeks thereafter	$	ECG performed every 48 weeks starting at visit V9
	Surrogate endpoint analysis performed and filed for initial market approval under Subpart H	*	Liver biopsy performed at approximately 4 years (visit V13) and in the case of suspicion of cirrhosis

Figure 2: PREGNANCY TESTING SCHEDULE FOR WOMEN OF CHILDBEARING POTENTIAL



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AASLD	American Association for the Study of Liver Diseases
ACR	albumin–creatinine ratio
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ANCOVA	Analysis of Covariance
ApoAI	apolipoprotein AI
ApoAII	apolipoprotein AII
ApoB	apolipoprotein B
ApoCIII	apolipoprotein CIII
AST	aspartate aminotransferase
AT	aminotransferase
ATP	Adult Treatment Panel
BMI	body mass index
BP	blood pressure
BUN	blood urea nitrogen
Bx	biological assessment visit
CA	competent authorities
CEC	Clinical Events Committee
CFR	Code of Federal Regulations
CPK	creatine phosphokinase
CRN	Clinical Research Network
CRO	Clinical Research Organization
CRP	C-reactive protein
CSR	Clinical Study Report
CYP	cytochrome P450
DDI	drug-drug interaction
DILI	drug-induced liver injury
DSMB	Data Safety Monitoring Board
DSUR	Development Safety Update Report
EASL	European Association for the Study of the Liver
ECG	electrocardiogram
eCRF	electronic case report form
EES	efficacy evaluable sample
eGFR	estimated glomerular filtration rate
EOS	end of study
EOT	end of study treatment
FDA	Food and Drug Administration
FFA	free fatty acid
FIB-4	fibrosis 4 score
FITT	full intent-to-treat set
FLI	fatty liver index
FPFV	first patient first visit

FSS	full safety set
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GLP1	glucagon-like peptide 1
HbA1c	hemoglobin A1c
HBsAg	hepatitis B surface antigen
HCC	hepatocellular carcinoma
HCV	hepatitis C Virus
HDL-C	High-density lipoprotein cholesterol
HIV	human immunodeficiency virus
HOMA-IR	homeostasis model assessment of insulin resistance
hPPAR	human peroxisome proliferator-activated receptor
HRT	Hormonal replacement therapy
HSC	hepatic stellate cells
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
INR	international normalized ratio
IP	investigational product
IQR	InterQuartile Range
IR	insulin resistance
IRB	Institutional Review Board
ITT	intent-to-treat
IXRS	Interactive Voice/Web Response System
LDL-C	Low-density lipoprotein cholesterol
LPLV	last patient last visit
[redacted]	[redacted]
LTTP	Long-term Treatment Period
M2	anti-inflammatory macrophages
MedDRA	Medical Dictionary for Regulatory Activities
MELD	model end stage liver disease
NAFL	nonalcoholic fatty liver
NAFLD	nonalcoholic fatty liver disease
NAS	NAFLD Activity Score
NASH	nonalcoholic steatohepatitis
NCEP ATP III	National Cholesterol Education Program's Adult Treatment Panel III
PBC	Primary Biliary Cholangitis
PD	pharmacodynamic
PK	pharmacokinetic
PPAR	peroxisome proliferator-activated receptor
PPS	per protocol set
PT	prothrombin time
PUFA	polyunsaturated fatty acids
QD	once daily
QTc	corrected QT
SADR	serious adverse drug reaction
SAE	serious adverse event
SAF	steatosis-activity- fibrosis

SAP	Statistical Analysis Plan
SBx	screening biological assessment visit
SF-36	36-Item Short-Form Health Survey
SGLT2	sodium/glucose cotransporter 2
SOP	Standard Operating Procedure
SS	safety set
SUSAR	suspected unexpected serious adverse reactions
SVx	Screening Visit x
TLC	therapeutic lifestyle change
TNF□	Tumor Necrosis Factor-alpha
UDCA	UrsoDeoxyCholic Acid
ULN	upper limit of normal
UV-LLNA	UV- Local Lymph Node Assay
Vx	Visit x
WOCBP	women of childbearing potential

1. INTRODUCTION

1.1. NONALCOHOLIC STEATOHEPATITIS

Nonalcoholic fatty liver disease (NAFLD) is a spectrum of disorders characterized by excessive fat accumulation in the liver (steatosis). Nonalcoholic steatohepatitis (NASH) defines a subgroup of NAFLD where steatosis coexists with hepatocyte injury and inflammation (steatohepatitis), with or without fibrosis.

Nonalcoholic steatohepatitis is considered by the European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Diseases (AASLD) as an increasing public health issue owing to its close epidemiological association with the worldwide epidemic of obesity and type 2 diabetes.

The prevalence of NAFLD in the general population assessed by ultrasonography is 20% to 30% in Europe. A similar prevalence of 15% to 25% was documented histologically by postmortem studies. A high prevalence of histological NAFLD has been described in apparently healthy liver donors: 12% to 18% in Europe and 27% to 38% in the US. Furthermore, with a sensitive technique such as magnetic resonance spectroscopy, 34% have NAFLD.

Interestingly, 39% of newly diagnosed cases of chronic liver disease had NAFLD, making NASH one of the top causes of liver diseases in Western countries. Using the histological definition of NASH, recent studies have shown a high prevalence of NASH among NAFLD cases: 43% to 55% in patients with increased aminotransferases (ATs), 49% in morbidly obese patients, and 67% in a subset of patients with incident chronic liver disease. Finally, in apparently healthy liver donors the prevalence of NASH ranges from 3% to 16% in Europe and from 6% to 15% in the US.

The commonest cause of NASH is primary NAFLD-associated insulin resistance and its phenotypic manifestations, namely excess weight/obesity, visceral obesity, type 2 diabetes, hypertriglyceridemia, and arterial hypertension. A causal association has been suggested by longitudinal studies showing a chronological association between the progression of insulin resistance, the metabolic syndrome, and the occurrence of NAFLD/NASH.

1.2. PATHOPHYSIOLOGICAL PROCESS OF NONALCOHOLIC STEATOHEPATITIS

A widely described model suggests that the development of NAFLD into NASH requires several 'hits' or insults.[1,2] According to this model, increased hepatic levels of free fatty acid (FFA) consequent to impaired insulin sensitivity in the liver and peripheral tissues may serve as the first hit. The increased hepatocyte FFA load would further increase insulin resistance (IR), steatosis, oxidative stress with lipid peroxidation, endoplasmic reticulum stress, resulting in inflammatory cell accumulation and activation into the liver (second hit). This finally leads to hepatocyte growth arrest or apoptosis, which activates hepatic progenitor cells and associated bile ductular proliferations, cells that initiate inadequate repair by producing a diverse range and high concentrations of profibrogenic cytokines and growth factors that activate hepatic stellate

cells (HSC) and perivascular or portal fibroblasts. The activated HSC themselves can release chemotactic factors that recruit inflammatory cells, creating a deleterious feedback inflammatory loop that leads to fibrogenesis. Collagen and other extracellular matrix components accumulate within the liver, which may result in distortion of the hepatic architecture and finally cirrhosis. Thus, in this "multiple-hit" model IR can be considered as the first step on the pathogenic road leading to NASH, fibrosis and cirrhosis.

However, this "multiple-hit" model has been recently challenged by data suggesting that mechanisms that can drive disease progression can also induce steatosis. Oxidative stress and gut flora/cytokines can induce steatosis as well as necroinflammation and fibrosis. Free fatty acids can initiate hepatocyte apoptosis in addition to being esterified to triglycerides. Endoplasmic stress can also lead to steatosis, oxidative stress, and apoptosis. Since all these mechanisms are important in obesity and IR, it would seem likely that they are the true "first hits" leading to increased hepatic FFA flux and oxidative-, endoplasmic reticulum-, and cytokine-mediated stress that result in both steatosis and progressive liver damage. Steatosis should therefore be considered part of the liver's early "adaptive" response to stress, rather than a first hit in disease progression. Accordingly, while in some situations its severity may act as a biomarker of ongoing injurious and fibrotic mechanisms resulting in disease progression, it should not be considered a sole therapeutic target. Instead attention should be paid on the mechanisms of cellular injury and fibrosis – the "second hits."

Oxidized by-products are harmful adducts that can cause liver injury, resulting in subsequent fibrosis.[3] Lipid peroxidation and oxidative stress up-regulate liver fibrosis via activation of stellate cells and increased production of Transforming Growth Factor-beta.[4] Over expression of uncoupling proteins has been associated with a reduction in generation of reactive oxygen species and Kupffer cell activation, which might attenuate injury in NAFLD. In addition to insulin resistance, several authors have shown that leptin contributes to an insulin-resistant state and might even stimulate fibrogenesis in animal models of NAFLD.[5]

Inflammatory mediators have been implicated in the progression of NAFLD and are the focus for new therapeutics. Pro-inflammatory transcription factors such as Nuclear Factor kappa B (NF-κB) are often elevated in patients with NASH.[6] Adiponectin decreases fatty acid oxidation and inhibits hepatic gluconeogenesis.7 Both human and mouse models have demonstrated that lower adiponectin levels are associated with increased severity of hepatic inflammation.[8,9] Tumor Necrosis Factor (TNF)α is an inflammatory mediator largely produced by macrophages, but also elaborated by other cells including adipocytes and hepatocytes.[1,10] Elevated levels of TNFα have been detected in obese patients with insulin resistance and NASH.[11,12] TNFα-mediated hepatic injury results from inhibition of mitochondrial electron transport and release of reactive oxygen species that stimulate lipid peroxidation.[10]

Recently, scientists have focused on the role of Kupffer cells in the pathogenesis of NAFLD. Kupffer cells are the resident macrophages of the liver and function in both innate and adaptive immunity as active phagocytosing agents and antigen-presenting cells (via toll-like receptors) to T-cells. Finally, the proapoptotic gene Bax is upregulated in patients with NASH and alcoholic liver disease.[13] Additionally, caspase levels, by- products of cellular apoptosis, are also increased in these groups of patients.

1.3. ELAFIBRANOR: RATIONALE FOR A MIXED PPAR ALPHA/DELTA AGONIST IN NASH

The GENFIT drug candidate, elafibranor, and its main active circulating metabolite, GFT1007, are dual peroxisome proliferator-activated receptor (PPAR)α/δ modulators with preferential activity on PPARα over PPARδ (about fivefold more potent on human PPAR [hPPAR]α than on hPPARδ). The PPARδ properties of elafibranor and GFT1007 have been demonstrated in both human skeletal muscle cells (a pure PPARδ response) and human hepatocytes (a mixed PPARα/δ response).

The PPARα receptors are most prominently expressed in the liver and can be activated by drugs of the fibrate class. Activation results in increased uptake and oxidation of FFAs, increased triglyceride hydrolysis and upregluation of apolipoprotein (Apo)A-I and ApoA-II. The net effect is fatty acid oxidation, decrease in serum triglycerides, a rise in high-density lipoprotein cholesterol (HDL-C) levels, and an increase in cholesterol efflux. The PPARα activation has also anti-inflammatory effects via inhibition of COX2, IL-6, and C-reactive protein (CRP). Some PPARα compounds have proved their effectiveness in animal models like Methionine-Choline-Deficient diet model or CCl4 in reducing the steatosis. However, clinical trials with fibrates in human NASH have been unimpressive. For example in a pilot study, 12 months treatment with clofibrate in 16 patients with NASH and elevated triglycerides had no impact on liver enzyme elevation or triglycerides levels.[14]

The PPARδ appears to be a powerful metabolic regulator, with actions on fat, skeletal muscle, liver, and heart. Its activation enhances fatty acid transport and oxidation, improves glucose homeostasis via improved insulin sensitivity and inhibition of hepatic glucose output, turns off macrophage inflammatory responses, and dramatically increases circulating HDL-C levels. Thus selective PPARδ agonists have the potential to target multiple components of the metabolic syndrome, including obesity, dyslipidemia, hypertriglyceridemia insulin resistance, and probably NASH.

Accordingly, PPARδ ligands also show promise in chronic inflammatory models of hepatotoxicity.[15] Notably, biomarkers of liver toxicity, including serum alanine aminotransferase (ALT), hepatic TNFα, TNF-like weak inducer of apoptosis receptor, were all higher in carbon tetrachloride-treated PPARδ knockout mice compared to wild-type mice. GW0742 reduced serum ALT, TNFα, S100A6, MCP1, and TNF-like weak inducer of apoptosis receptor in wild-type mice, but not PPARδ knockouts.

Finally, in a short clinical trial, a pure PPARδ agonist, GW501516, has demonstrated efficacy on liver fat content while improving insulin resistance and decreasing γGT.[16]

Considering the emerging role of Kupffer cells in the pathogenesis, 2 recent publications identified PPARδ as a crucial signaling receptor controlling the phenotypic switch between classical pro-inflammatory and alternative anti-inflammatory (M2) macrophages.[17,18] These studies demonstrate that PPARδ encourages macrophages toward the alternative M2 phenotype, which improves fatty acid metabolism, insulin sensitivity, and suppresses inflammation. The finding raise the possibility that small molecule agonist of PPARδ may be effective therapeutic targets for the treatment of chronic inflammation in the liver.

The match between the activation of PPARα and PPARδ in the liver may thus improve NASH. Accordingly, in several well-established experimental models of NAFLD/NASH and liver fibrosis, treatment with elafibranor confers liver protection both in preventive and therapeutic approaches on established pathologies. These effects have been demonstrated through plasma and hepatic markers, as well as liver macro- and micro- histological examination. These studies have shown that elafibranor acts on several mechanisms involved in NASH pathogenesis: steatosis, inflammation, and fibrosis pathways. Complementary studies have demonstrated that both PPARα-dependent and PPARα-independent mechanisms participate in the beneficial effects of elafibranor on NAFLD/NASH.

1.4. SUMMARY OF NONCLINICAL STUDIES

1.4.1. Pharmacology

Besides hepatoprotection, the efficacy of elafibranor has been assessed in numerous pharmacological preclinical models of metabolic disorders. Briefly, in experimental models of type 2 diabetes, elafibranor has insulin-sensitizing and glucose lowering properties. In db/db mice, a 28-day treatment with elafibranor produced a dose-dependent decrease in fasting plasma glucose and glycated hemoglobin (HbA1c), comparable to the effect of rosiglitazone. However, in contrast to the PPARγ reference agonist, elafibranor did not increase plasma adiponectin, thus ruling out a PPARγ -mediated effect on adipose tissues. Similarly, in ob/ob mice, elafibranor ameliorated plasma glucose and insulin levels without modulating plasma adiponectin or inducing PPAR target genes in adipose tissues.

Besides its effects on NAFLD/NASH and type 2 diabetes, oral treatment with elafibranor in a mouse model of dyslipidemia potently reduced plasma triglycerides and total cholesterol through the induction of PPARα target genes in the liver and by reduction of ApoCIII gene expression. In parallel, elafibranor increased plasma HDL-C levels more potently than the PPARα reference compound fenofibrate. The chronic treatment of these mice fed a high fat diet with elafibranor prevented the development of atherosclerotic plaques in the aorta.

1.4.2. Safety pharmacology

Any potential effect on the cardiovascular, respiratory, and central nervous system has been assessed and no safety issue was identified.

1.4.3. Absorption/distribution/metabolism/excretion studies (ADME)

In animal studies, elafibranor was well and rapidly absorbed although absolute bioavailability was moderate (about 20% to 40%). Elafibranor is extensively metabolized and the activity is mainly carried by the active metabolite GFT1007. In rat and dog, maximal plasma concentrations and exposure for both elafibranor and GFT1007 linearly increase with the dose after single or repeated administrations. Elafibranor and its metabolites are rapidly cleared from the plasma and they are totally excreted by both fecal and renal route within 48 hours. In the rat elafibranor and/or its metabolites are rapidly excreted into the bile and undergo an extensive entero-hepatic cycle giving support for liver targeting of elafibranor

and/or GFT1007. The distribution study in the rat supports the liver targeting of elafibranor and/or its metabolites.
In vitro elafibranor does not inhibit cytochrome p450 (CYP)1A2, CYP3A4, and CYP2D6 with moderate inhibition of CYP2C9 and weak inhibition of CYP2C8, CYP2C19, and CYP4A11. GFT1007 does not produce any inhibition of the CYP450 isoforms 1A2, 3A4, 2C19, and 2D6, and only weak inhibition of CYP2C8 and CYP2C9. Both molecules also show weak inhibition of CYP3A4/5, but only with midazolam as substrate. Thus, the risk of drug-drug interaction due to an inhibition of the main cytochromes involved in drug metabolism should be limited. Potential interaction with CYP2C9 metabolized drugs has been assessed through a clinical study (GFT505-112-8) designed to evaluate potential pharmacokinetic (PK) interaction of elafibranor 120 mg administered for 14 days alone or with a single administration of warfarin. This study demonstrated that elafibranor administration did not affect the PK profile of warfarin (R-warfarin and S-warfarin).

A protein binding study showed that elafibranor and GFT1007 were highly bound to human serum albumin. The risk of drug-drug interaction due to albumin binding should be limited since this binding is not saturable.

In vitro studies have been performed to determine whether elafibranor (GFT505) and it principal metabolite GFT1007 are substrates and/or inhibitors of major drug transporters, in order to assess the potential for drug-drug interaction (DDI). Based on the results of the OATP1B3 transporter inhibition assay, elafibranor (GFT505) has recently been assessed in a follow-up clinical DDI study with the OATP1B3-sensitive substrate, atorvastatin.

For the other drug transporters studied, the interaction observed does not require follow-up studies based on current regulatory guidance.

The metabolic stability and metabolism pathways of elafibranor (GFT505) have been studied on liver microsomes and in primary hepatocytes from rat, dog, mouse, monkey, and human. There was no evidence of the formation of unique human metabolites or metabolites formed at disproportionately higher levels in human hepatocytes than in any other species.

An in vivo study has been performed to compare the bioavailability of ^{14}C-GFT505 in the rat, dog, minipig, and monkey. This study showed that in all species ^{14}C-GFT505 is rapidly absorbed, although absolute bioavailability was moderate (about 20% to 40%).

1.4.4. Toxicology

1.4.4.1 Mutagenicity and genotoxicity

The toxicology program performed according to International Council for Harmonisation (ICH) guidelines demonstrates that elafibranor has no genotoxic or mutagenicity potential.

1.4.4.2 Acute toxicity

According to acute toxicity studies results, it can be concluded that elafibranor is extremely safe when

administered as single oral doses in rat and mouse, since no sign of toxicity was detected up to the dose of 1000 mg/kg.

1.4.4.3 Repeated dose toxicity studies

The safety of elafibranor has been assessed in multiple preclinical toxicology studies with repeated-dose oral administration for up to 6 months in rats and 12 months in monkeys. Moreover, two-year repeated-dose carcinogenicity studies in mice and rats have been completed.

The only consistent safety concern raised by these studies is the expected PPARα-associated hepatomegaly, hepatocellular hypertrophy, and liver carcinoma in rodent species (mice and rats). However, it is well known that, compared to nonhuman primates and humans, rodents are highly sensitive to PPARα agonist induced peroxisome proliferation and associated liver side effects. Thus, available information on this class of drug which includes marketed fibrates together with the lack of any liver side effects in monkeys treated with high doses of elafibranor for 1 year support the nonrelevance to human.[19] Overall, these studies did not reveal any other safety issues up to the highest doses tested. Notably, elafibranor did not have any of the known PPARγ-related concerns such as excess in weight gain, hemodilution, edema, cardiomegaly, adiponectin induction, or urinary bladder carcinoma.

1.4.4.4 Phototoxicity studies

The phototoxic potential of elafibranor has been assessed by the in vitro 3T3 NRU phototoxicity test and the UV- Local Lymph Node Assay (LLNA) test in mice. Elafibranor (GFT505), but not its major metabolite GFT1007, showed UVA-dependent cytotoxicity in vitro. The UV-LLNA test was performed in mice with oral dosing for 3 days at up to 800 mg/kg/day elafibranor. Although a very conservative no observed effect level (NOAEL) was set at 400 mg/kg/day based on isolated findings at the highest dose, it is considered that data are more in favor of an absence of phototoxic effect, given the tissue distribution of elafibranor (GFT505), and absence of phototoxicity signal in the clinical studies.

1.5. CLINICAL STUDIES

1.5.1. NASH

A Phase I program to assess the safety and tolerability as well as the PK profile of elafibranor has been conducted through 12 completed clinical trials, and 5 still ongoing. A total of 561 healthy lean subjects, 60 overweight or obese subjects, and 12 patients with type 2 diabetes, 6 with end stage renal disease and 20 with hepatic impairment (Child-Pugh class A, B or C) have been randomized to date in the completed trials. Elafibranor daily doses ranged between 5 mg and 360 mg, with a treatment duration up to 16 days.

A Phase 2 program was initiated to assess the safety and efficacy profile of elafibranor in subjects with cardiometabolic disorders and NASH. To date, 5 Phase 2a studies have been completed, in which 297

subjects were randomized: 37 with mixed hyperlipidemia (type IIb Frederickson); 94 with atherogenic dyslipidemia and abdominal obesity; 47 with impaired glucose tolerance and abdominal obesity; 97 with diabetes mellitus type II; and 22 with insulin resistance and abdominal obesity. A Phase 2b study has also been completed, in which 274 subjects with NASH were randomized. In the Phase 2 program, the elafibranor daily doses ranged between 30 mg and 120 mg, with a maximum treatment duration of 12 months.

A Phase 2a randomized, open-label, sequential cohort study (GFT505E-218-1) will assess the PK and pharmacodynamic (PD) profile and the safety and tolerability of two dose levels of GFT505 (80 mg and 120 mg) in children and adolescents, 8 to 17 years of age, with NASH. In this study, subjects will receive 80 or 120 mg of GFT505 once daily for 12 weeks. The study consists of two paediatric patient cohorts with NASH which will be dosed sequentially. Cohort 1 will consist of +/- 12 subjects who are ≥12 to ≤17 years of age. Once 10 subjects in cohort 1 have been evaluated for PK and safety through Visit 4 (30 days) by an independent Data Safety Monitoring Board (DSMB), enrollment will be open to subjects ≥8 to ≤11 years of age. Cohort 2 will consist of +/- 8 subjects who are ≥8 to ≤11 years of age.

At time of DSUR data lock point (31 July 2019), 1 subject (≥12 to ≤17 years of age) had been enrolled and exposed to at least one administration of GFT505.

A Phase 2 study (GFT505-219-8) to evaluate the effect of a 6-week elafibranor (120 mg) treatment administered once daily on hepatic lipid composition in subjects with nonalcoholic fatty liver (NAFL) is currently ongoing. This study intends to achieve mechanistic information about the mode of action of elafibranor on the (lipid) metabolism in the human fatty liver. Subjects with NAFL will receive 120 mg of GFT505 or placebo once daily for 6 weeks in randomized order in a crossover design. Overall, 16 subjects with NAFL are intended to be included.

For additional information see Investigator's Brochure.

1.5.2. PBC

Based on the mechanism of action of elafibranor, and on the relevant efficacy and safety data collected to date, specifically on decrease in ALP and inflammation markers, a Phase 2a study has been launched in PBC has been completed, under IND 132202, filed in September 2016. The aim of this study was to validate the efficacy of elafibranor on ALP decrease in this patient population, and to confirm its safety in a population with PBC. This study was designed to compare the effect of daily oral administration for 12 weeks of GFT505 80 mg and 120 mg on changes in serum alkaline phosphatase (ALP) to that of placebo in subjects with PBC and inadequate response to ursodeoxycholic acid (UDCA).

For additional information see Investigator's Brochure.

1.6. CONCLUSION

Clinical data confirmed the beneficial effect of elafibranor in NASH patients, with efficacy on histology associated with improvement on insulin resistance, and with relevant reductions in markers of liver injury

such as GGT and ALT, and in inflammatory markers. It demonstrated also improvement in lipid profile resulting in a beneficial balance between pro and anti-atherogenic markers.

Moreover at the last DSUR cut-off date (31 July 2019), 25 clinical studies with elafibranor have been conducted or are ongoing (in which a total of 3245 subjects have been randomized, including an estimated 2206 subjects exposed to elafibranor. In general, the treatment was well tolerated. No interaction, medication errors, or abuse/misuse cases have been reported to this date. See Section 6.6 for further information.

For additional information see Investigator's Brochure.

1.7. RATIONALE FOR STUDY POPULATION

Given the natural fluctuation of the disease for patients with mild NASH (NAS score of 3), phase IIb study results have clearly highlighted that only NASH patients with moderate to severe disease (NAS score≥4) should be treated.

Regarding fibrosis, available data from meta-analyses demonstrate that NASH patients are at greatest risk of progression to advanced fibrosis, cirrhosis, and liver outcomes. Patients with NASH develop progressive fibrosis in 25% to 50% of individuals over 4-6 years, while 15% to 25% of individuals with NASH can progress to cirrhosis.[20] In another study, with a mean follow-up of 13 years, 13.3% of NASH patients with mild to moderate fibrosis (stage 1-2) and 50% of patients with fibrosis stage 3 at inclusion developed cirrhosis.[21]

Considering these data, it is reasonable to include NASH patients with any stage of fibrosis (stage 1 to 3) in the Phase III program, from both safety and prospect for benefit standpoints. However, since in patients with NASH and advanced fibrosis (F2-F3) the probability of developing cirrhosis is much higher than in patients with early fibrosis (F1), the population evaluated for the long-term outcome needs to be based on the advanced fibrosis patients in order to enhance the chances of demonstrating a benefit within a reasonable timeframe.

Accordingly, the target population for the analysis of surrogate endpoint and liver outcomes will be NASH patients with advanced fibrosis (F2-F3). The enrollment of patients with advanced fibrosis for the evaluation of long-term outcomes including progression to cirrhosis should ensure that an expected number of events, calculated based on progression rate for each fibrosis stage, are obtained. Based on the literature,[21,22,23,24,25] in patients with NASH and advanced fibrosis (F2-F3) this progression rate can be estimated at 8% per year for fibrosis stage 3 and 6% per year for fibrosis stage 2, thus an average of 7% for advanced fibrosis.

As a conservative approach, no supplementary percentage was added to the estimated progression rate to histological cirrhosis (7%) for all the other events of the composite endpoint not linked to cirrhosis. Generally, liver decompensation events occur only when cirrhosis is present and the progression rate to the other events is expected to be very low.

A limited number of NASH patients with fibrosis stage 1 and associated comorbidities known to be at risk of fast disease progression will be included in the study as an exploratory group.

Enrollment of female patients will be capped at 40% in each group for this study to mirror the higher prevalence of NASH in males compared to females.[26]

1.8. JUSTIFICATION OF THE SELECTED DOSE

The results obtained in the Phase IIb study evaluating the resolution of NASH clearly demonstrated the superiority of the elafibranor dose of 120 mg over 80 mg on the histological endpoint, regardless of the population selected (Intent-To-Treat [ITT] or Full Analysis Set) or the subgroup tested, indicating that the dose to be used for the Phase III trial should be 120 mg.

To support this assumption, a dose-response modeling was performed based on data obtained in the Phase I clinical program with 14-day repeated dose studies ranging from 5 mg to 360 mg daily dose. In this model, the studied response was the change at endpoint versus baseline in biochemical parameters known to be associated in a dose-dependent manner with elafibranor exposure, such as liver enzymes (ALT, GGT, alkaline phosphatase), plasma lipids (triglycerides, LDL-C, HDL-C) or serum creatinine. Based on this modeling, the optimum dose was consistently assessed as a value of 118 mg. Therefore, given its good safety profile and evidence of efficacy, both supported by the dose-response modeling, 120 mg elafibranor appears to be the most appropriate dose for the upcoming Phase III trial.

1.9. RATIONALE FOR EFFICACY ENDPOINT

1.9.1. Primary endpoint for application under conditional approval

Steatohepatitis is indirectly associated with reduced hepatic survival in NAFLD.[21,27] It drives fibrogenesis, a slow process of hepatic scar formation that can result in cirrhosis and its deadly complications such as liver failure, portal hypertension, and hepatocellular carcinoma. Consequently, clearance of steatohepatitis,[28] i.e., reversal to a normal liver or to steatosis without steatohepatitis – a condition not associated with increased hepatic morbidity or mortality – is expected to improve hepatic prognosis. Natural history studies are now available showing that patients with steatohepatitis but not those with steatosis only (i.e., nonNASH NAFLD) are the ones that progress to cirrhosis and liver-related outcomes. This forms the basis for "resolution of NASH" as a desirable outcome of therapy in the short-term; a concept widely embraced by the academic community and expressed in several scientific society endorsed position papers.[29,30] Based on the recently published recommendations from this workshop,[30] resolution of NASH with no worsening of fibrosis may be an acceptable surrogate endpoint suitable for a Phase III enrolling patients with NASH and fibrosis. Based on recent data that have shown that fibrosis stage of 2 or more is related to liver-related mortality,[22] the "no worsening of fibrosis" should be no progression of one stage in fibrosis.

1.9.2. Primary endpoint for clinical outcome (postapproval confirmation)

The primary endpoint of the Long-term Treatment Period (LTTP) of the study is to evaluate the effect of elafibranor on the progression to cirrhosis, all-cause mortality, and liver-related clinical outcomes as measured by the onset of any of the listed adjudicated events (clinical outcomes composite endpoint).

Primary endpoint events include overall mortality, progression to cirrhosis, and the full list of portal hypertension/cirrhosis related events (liver transplantation, model end stage liver disease (MELD) score ≥15, and hospitalization due to occurrence of hepatic encephalopathy or variceal bleeding, spontaneous bacterial peritonitis, and uncontrolled ascites requiring treatment).

Singh et al. recently provided a thorough meta-analysis of paired biopsy studies to obtain the most accurate estimate of the fibrosis progression rate in a large cohort of patients with NAFLD.[25] Over 2145.5 person-years of follow-up evaluation, 33.6% had fibrosis progression, 43.1% had stable fibrosis, and 22.3% had an improvement in fibrosis stage. Overall, the annual fibrosis progression rate in a population of patients with NAFLD who had stage 0 fibrosis at baseline was 0.07 stage/year compared to 0.14 stage/year in a population of patients with NASH. In another study of 108 patients, no significant difference in the proportion exhibiting fibrosis progression was found between those with NAFLD or NASH.[31] In the whole cohort, the mean annual rate of fibrosis progression was 0.08 stage/year.

Based on the literature, in patients with NASH and advanced fibrosis (F2-F3), the probability of developing cirrhosis can be estimated at 8% per year for fibrosis F3 and 6% per year for fibrosis F2.[21,22,23,24,25]

In conclusion, the difference in progression to cirrhosis, other liver-related events, and total deaths between treatment and control groups can be considered as a potential clinically meaningful outcome measure for clinical trials. This long-term outcome including progression to cirrhosis is considered acceptable,[30] and required in a postapproval study for treatments approved under conditional approval.

1.10. RATIONALE FOR STUDY DURATION

In accordance with the AASLD and EASL recommendations, 72-weeks of treatment have been defined for the first stage of the study in order to demonstrate the efficacy of elafibranor on resolution of NASH without worsening of fibrosis.

The estimated duration of the LTTP is based on a 7% probability of patients with NASH and moderate and advanced fibrosis (F2-F3) developing cirrhosis or other liver-related events as determined from recently published data [21,22,23,24,25] and the available data of the mortality risk in this patient population.[32,33]

1.11. RATIONALE FOR SAFETY MONITORING

The safety of use of the dose of 120 mg/d of elafibranor during the proposed trial is supported by the chronic toxicity studies and previous Phase I and Phase II trials. Indeed, the toxicology package of elafibranor does not reveal any major safety concern, based on the conclusion that elafibranor-induced liver toxicity in rodents is not relevant to nonprimates (no evidence of liver toxicity in monkeys after 1 year but improvement of liver function markers) and humans (consistent improvement of liver function markers in all Phase II trials). These toxicology results and conclusions are on-line with the extensive literature on the

liver effects of PPAR agonists.

An independent DSMB will be established in order to review the progress of the study and to perform a safety data review (as defined by the DSMB Charter) on a regular basis during the trial to protect patient welfare and preserve study integrity.

Knowing the risks associated with NASH and disease progression, specific attention will be paid to potential hepatotoxicity, liver-related and cardiovascular events.

Given the known effect of elafibranor on serum creatinine increase, special attention will be paid to all the renal safety markers (plasmatic or urinary parameters), including but not limited to albumin-creatinine ratio, cystatin C, neutrophil gelatinase-associated lipocalin (N-Gal), N acetyl β D-glucosaminidase β-NAG, kidney injury molecule-1 (KIM-1). Serum creatinine, modification of diet in renal disease (MDRD) derived estimated glomerular filtration rate (eGFR), and the results of urinalysis (dipstick) will be reported at each visit, as well as blood urea nitrogen. The other markers (plasmatic or urinary) will be assayed in batch and will be reviewed on an ongoing basis through regular safety reviews by the DSMB which includes a nephrologist.

Assays of many other markers are scheduled in order to monitor liver function markers, cardiac safety markers, and to follow up the cardiovascular profile which is known to be at risk in NASH patients.

For cardiac safety, troponin-T and NT-ProBNP will be followed and reviewed on a regular basis by the DSMB. In addition, electrocardiogram (ECG) and blood pressure (BP) will be routinely monitored throughout the study.

Liver function will be monitored throughout the study, by assessment of liver enzymes, bilirubin (total and conjugated), alkaline phosphatase, and international normalized ratio (INR) reported at each visit.

In addition, even if no safety concern has been revealed in the previous clinical program, all the biological parameters that are known to be affected by PPAR agonists will remain monitored in the Phase III trials, such as hematological parameters, adiponectin, or homocysteine.

During the LTTP, patients will be monitored by clinical and biological assessment. A FibroScan® measurement and noninvasive markers assessment will be performed every 24 weeks, and if cirrhosis is suspected, a confirmation by liver biopsy will be performed.
For additional information see Investigator's Brochure.

2. TRIAL OBJECTIVES

To assess the efficacy and safety of elafibranor as compared to placebo in adult NASH patients with fibrosis stage 2 or 3 (F2-F3), the primary and secondary objectives are as follows:

2.1. PRIMARY OBJECTIVES

2.1.1. Surrogate endpoint analysis

To evaluate the efficacy of elafibranor 120 mg QD for 72 weeks versus placebo on resolution of NASH without worsening of fibrosis.

- Resolution of NASH is defined as the disappearance of ballooning and disappearance or persistence of minimal lobular inflammation (grade 0 or 1) with an overall pattern of injury not qualifying for steatohepatitis.
- Worsening of fibrosis is evaluated using the NASH Clinical Research Network (CRN) fibrosis staging system and defined as progression of at least 1 stage.

2.1.2. Long-term endpoint

To evaluate the efficacy of elafibranor 120 mg QD versus placebo on clinical outcomes described as a composite endpoint composed of death due to any cause, histological liver cirrhosis, and the full list of portal hypertension/cirrhosis related events:

- Liver transplantation
- MELD score ≥15 for patients with baseline MELD score ≤12
- the onset of:
  - variceal bleed requiring hospitalization,
  - hepatic encephalopathy defined as West Haven/Conn score ≥2 and requiring hospitalization,
  - spontaneous bacterial peritonitis,
  - ascites requiring treatment.

2.2. KEY SECONDARY OBJECTIVES – AT SURROGATE ENDPOINT ANALYSIS

To assess histological changes after 72 weeks of treatment, at the time of surrogate endpoint analysis, on the following endpoint:

- Percentage of patients with improvement of fibrosis of at least 1 stage according to NASH CRN scoring.

To assess the clinical benefit after 72 weeks of treatment on the following metabolic endpoints:

- Changes from baseline in triglycerides, Non-HDL cholesterol, HDL cholesterol, LDL cholesterol,

HbA1c (in diabetic patients), HOMA-IR (in non-diabetic patients)

2.3. OTHER SECONDARY OBJECTIVES

- To assess histological changes after 72 weeks of treatment and at the end of the LTTP on the following endpoints:
  - percentage of patients with resolution of NASH without worsening of fibrosis (at the end of LTTP)
  - percentage of patients with improvement of fibrosis of at least 1 stage according to NASH CRN scoring (at the end of LTTP)
  - percentage of patients with improvement of fibrosis of at least 1 stage according to NASH CRN scoring without worsening of NASH
  - percentage of patients with no worsening of fibrosis and no worsening of NASH
  - percentage of patients with resolution of NASH and improvement of Fibrosis
  - percentage of patients with at least a 1 point improvement in histological scores (NASH CRN scoring: NAS [sum of steatosis, hepatic ballooning and lobular inflammation], steatosis, hepatic ballooning, lobular inflammation), fibrosis (NAFLD Ishak scoring system), or portal inflammation
  - percentage of patients with improvement of NAS of at least 2 points
  - percentage of patients with improvement of NAS of at least 2 points and with at least 1 point improvement in hepatic ballooning
  - percentage of patients with at least a 1 point improvement in disease activity score (sum of ballooning and lobular inflammation scores) according to NAS scoring and steatosis-activity- fibrosis (SAF) scoring
  - percentage of patients with at least a 1 point improvement in disease activity score (sum of ballooning and lobular inflammation scores) according to NAS scoring and with at least 1 point improvement in hepatic ballooning
  - percentage of patients with at least a 1 point improvement in disease activity score (sum of ballooning and lobular inflammation scores) according to SAF scoring and with at least 1 point improvement in hepatic ballooning
  - percentage of patients with at least 2 points improvement in disease activity score according to NAS scoring and SAF scoring
  - changes in NAS, fibrosis (using NASH CRN and NAFLD Ishak scoring system), steatosis, hepatic ballooning, lobular inflammation, portal inflammation and SAF activity score
  - changes in area of fibrosis (normalized Collagen Proportional area in %) by morphometry
- To assess the following endpoints at Week 72 and at the end of the LTTP:
  - changes in liver enzymes and liver markers
  - changes in noninvasive markers of fibrosis and steatosis
  - changes in lipid parameters
  - variation in body weight
  - changes in insulin resistance and glucose homeostasis markers
  - changes in inflammatory markers

- changes in cardiovascular risk profile as assessed by Framingham scores
- changes in liver stiffness by Fibroscan measurement
- changes in quality of life (36-Item Short-Form Health Survey [SF-36] questionnaire).

- To assess the onset to:
  - histological liver cirrhosis
  - death of any cause
  - any portal hypertension or cirrhosis related events
  - cardiovascular events
  - liver-related death events

2.4. EXPLORATORY OBJECTIVES

- To constitute a biobank for discovery and validation of biomarkers in NASH.

2.5. EXPLORATORY OBJECTIVES FOR F1 GROUP AND THE OVERALL POPULATION (WHATEVER THE FIBROSIS STAGE – F1, F2 OR F3)

- To explore, in F1 patients and in the overall population whatever the fibrosis stage (F1, F2 or F3), the same endpoints as for the primary and secondary objectives.

2.6. SAFETY SECONDARY OBJECTIVES

To assess the tolerability and safety of once a day administration of oral doses of elafibranor 120 mg:

- SAE, AE, AESI, physical examination, vital signs, medical history, ECG
- hematological parameters
- liver markers
- renal biomarkers (including urinalysis)
- cardiac biomarkers
- metabolic parameters
- other biochemical safety markers.

3. TRIAL DESIGN

This is a Phase III, randomized, double-blind, parallel groups, placebo-controlled study, evaluating the efficacy and safety of elafibranor 120 mg QD versus placebo in an adult NASH population with fibrosis.

The first double-blind 72-week Treatment Period will assess the efficacy and safety of elafibranor on the resolution of NASH without worsening of fibrosis at the surrogate endpoint efficacy analysis, followed by a LTTP to assess efficacy on progression to cirrhosis, all-cause mortality, and liver-related clinical outcomes as measured by the onset of any of the listed adjudicated events (see Section 2.1.2). The study will terminate upon the 456th patient (excluding exploratory F1 group [see below]) experiencing an event listed in the composite endpoint for long term efficacy evaluation.

It is planned to randomize patients to either active or placebo treatment in a 2:1 ratio, stratified by type 2 diabetes, gender (with a capping of women to 40%), and fibrosis stage. Additional patients with fibrosis stage 1 (10% of sample size calculated for the F2 and F3 patients) and high risk for progression of NASH will also be enrolled for exploratory purposes.

3.1. NUMBER OF PATIENTS

It is planned to randomize at least 2022 F2/F3 patients to either active (1348 patients) or placebo (674 patients) treatment in a 2:1 ratio. Up to 202 additional patients (a maximum level of 10% of the F2/F3 enrolled patients) with fibrosis stage of 1 and high risk for progression of NASH (NAS ≥5, F1 patients with at least 2 of the following conditions: persistent elevated (absence of normal ALT within the past year, obesity defined by a body mass index (BMI) ≥30, metabolic syndrome [National Cholesterol Education Program's Adult Treatment Panel III {NCEP ATP III definition}], type 2 diabetes, or HOMA-IR >6) will also be enrolled, and followed as an exploratory group. The F1 patients will not be included in the primary surrogate endpoint and final analysis or in the sample size calculation (detailed in Section 9.7). As such a total of at least 2224 patients will be enrolled, including the exploratory F1 group.

3.2. METHOD OF ASSIGNING PATIENT TO TREATMENT GROUP

Patients who satisfy all eligibility criteria will be randomly allocated to one of the following groups in a 2:1 ratio:

- Elafibranor 120 mg
- Placebo.

Randomization to treatment will be stratified to ensure balance of treatment allocation by the following 3 factors:

- Type 2 diabetes (yes, no)
- Gender (male, female) (with a capping of women to 40%)

- Fibrosis stage (F1, F2, F3) (capped to 202 F1 patients).

Treatment assignments will be made using an interactive voice/web response system (IXRS).

3.3. DOSE ADJUSTMENT CRITERIA

Not applicable. Patients will be randomized to a fixed dose with no allowance for dose adjustment.

3.4. DURATION OF STUDY PARTICIPATION

The estimated duration of the study will be approximately 96 months, based on 456 patients experiencing an event described in Section 2.1.2 at an assumed annual rate event of 7%. However, this may be redefined according to the actual occurrence of events (described in Section 2.1.2) during the confirmatory part of the study (LTTP).

3.5. STUDY PERIODS

The study will comprise 3 periods. The Screening Period (-12 to -1 weeks) will precede a 72-week double-blind First Treatment Period and a LTTP up to the occurrence of a prespecified number of events.

Study procedures are summarized in Table 1, Table 2, and Figure 1.

Schedule:

- Week -12 to Week -1 prior to Randomization: Screening Period (screening visits SV1 to SPV).
- Week 0 to Week 72: First Treatment Period with Elafibranor or placebo for 72 weeks (visits V1 to V7).
- Week 72 to end of study (EOS): LTTP with elafibranor or placebo until 456 patients experience an event listed in Section 2.1.2 (visits V8 to Vn).

3.6. SCREENING PERIOD (WEEK -12 TO WEEK -1)

3.6.1. Screening visits SV1 and SV2

The following screening procedures will be performed for all potential patients at SV1 conducted during the screening period and prior to randomization:

- Signature of informed consent witnessed by the Investigator or designated person. **Note**: The signature of the informed consent may also be performed before SV1.
- Patient number allocation via IXRS.
- Check medical history/demographics.
- Check inclusion/exclusion criteria (described in Section 4).
- Physical examination (described in Section 6.2.1).
- Adequate diet recommendations (described in Section 5.1.1 and APPENDIX II: Adequate diet

and lifestyle recommendations), alcohol restrictions (described in Section 5.1.2), and tobacco habits.
- Record vital signs (described in Section 6.2.3).
- Record height, weight, and waist circumference.
- Check concomitant/prior medication (within 6 months prior to Screening) (described in Section 7.12 and APPENDIX III: Permitted/non-permitted medication)
- Check if a liver biopsy with confirmed NASH and fibrosis is available, and, if so send sample for central confirmation of NASH diagnosis (described in Section 6.1.1.2). This historical diagnostic biopsy should be obtained within 6 months prior to the Screening Visit.
- Check AEs from time of Informed Consent Form (ICF) signature (described in Section 6 and Section 8).

The Screening biological assessment (SB1 will be scheduled at SV1).

If no diagnostic liver biopsy (within 6 months of SV1) is available, it is recommended to schedule an additional SV2 visit at least Week -4 prior to the planned Randomization V1, in order to obtain the results in time.

The following biological assessments (detailed in Table 2) will be performed at SB1:

- Blood samples (described in Table 2).
- Whole blood, plasma & serum bank samples (only if additional genetic and biomarker ICF signed).
- Urinalysis dipstick.
- Urinary pregnancy test (for women of childbearing potential only [WOCBP]).

If no historical values of AST, ALT, total bilirubin and INR meeting the requirements of within 8 weeks to 6 months of randomization visit are available, then SV1 and V1 must be scheduled at least 8 weeks apart in order to have 2 consecutive values for DILI adjudication.

In case of known cured hepatitis C virus (HCV) infection, HCV RNA testing can be done at SV1 without waiting for HCV Ab results.

If needed, a retesting of abnormal HbA1c, or creatine phosphokinase (CPK) results or additional testing of HCV RNA, may be performed during the screening window to determine the eligibility for the study as described in exclusion criteria 5, 12, 30, and 31 (see Section 4.2 and Section 3.11).

At visit SV1, preliminary entrance criteria will be reviewed. Potentially eligible patients will be asked if they agree to participate in the study and sign the ICF. Each patient who has signed the ICF will be allocated a patient number composed of 9 digits which is generated by the IXRS.

- First 3 digits corresponding to the ISO numeric country code (this number will be predefined),
- Next 3 digits corresponding to the site number (this number will be predefined),
- Last 3 digits corresponding to the numerical order of the patient entry at the study site.

A specific IXRS procedure manual will be provided to the Investigator.

3.6.2. Screening Visit SV2 (liver biopsy if required, Week -12 to recommended Week -4):

If no diagnostic liver biopsy within 6 months of SV1 is available, it is recommended to schedule an additional SV2 visit at least Week -4 for a liver biopsy to be performed (described in Section 6.1.1.1). Blood samples for coagulation (detailed in Table 2) will be taken and tested at a local laboratory prior to the liver biopsy. Liver biopsy samples will be sent for central confirmation of NASH diagnosis (described in Section 6.1.1.2).

During this visit AEs (from the time of signing the ICF) will also be checked (described in Section 6 and Section 8).

3.6.3. Screening Phone Visit SPV (Week -1):

Upon receipt of the NASH diagnosis confirmation and the SB1 or any retesting/additional testing results from the central laboratory, the Investigator should check the eligibility with inclusion/exclusion criteria.

If patient meets all inclusion criteria and none of the exclusion criteria (clinical, histological, and biological ones), the Investigator will inform the patient of his/her inclusion/noninclusion status by a phone call within 1 week prior to the Randomization Visit V1. In case of ineligibility, the patient should be contacted as soon as possible.

3.7. FIRST TREATMENT PERIOD (WEEK 0 TO WEEK 72)

Efficacy of elafibranor versus placebo on resolution of NASH without worsening of fibrosis will be evaluated in this first period treatment of 72 weeks.

The NASH will be evaluated for inclusion by a centrally-read liver biopsy taken within 6 months prior to Screening (if no historical biopsy is available for NASH diagnosis, a liver biopsy will be performed during the Screening Period) with:

- Presence of NASH, with at least a score of 1 in each component of the NAS (steatosis scored 0 to 3, ballooning degeneration scored 0 to 2, and lobular inflammation scored 0 to 3) AND NAS ≥4.
- Fibrosis stage 2 and 3.

A group of patients (n=202, 10% of each group) with F1 fibrosis, NAS ≥5, and concomitant cardiometabolic comorbidities, which are associated with rapid progression of the disease (listed in Section 3.1), will also be enrolled and followed as an exploratory group.

During these first 72 weeks of treatment, visits will be scheduled every 12 weeks. Clinical and biological evaluation will be performed during this First Treatment Period.

At the end of the 72-week treatment period, a biopsy will be performed for all the patients under treatment in order to evaluate the effect of elafibranor on the liver histology.

When at least the first 1023 randomized patients (F2-F3) complete Week 72 (or discontinue early from the study treatment), a surrogate endpoint analysis will be performed and potentially filed for initial market approval under Subpart H or conditional approval, (see Section 9.8.1 for details).

During the First Treatment Period the patients will return to the site for visits every 12 weeks (±1 week) from the Randomization Visit (V1); however the maximum time period between visits is to be 96 days due to the study drug supply provided to the patient.

A diagnosis of any event listed in the primary composite endpoint described in Section 1.9.2 will result in the permanent discontinuation of study drug and discontinuation from the study, following an end of study treatment (EOT) Visit as described in Section 3.9 and Section 5.2.2).

3.7.1. Randomization Visit V1 (Week 0):

Eligible patients will return to the site at the Randomization Visit V1 and then every 12 weeks in the First Treatment Period of the study until the first 72 weeks of treatment (V7) (surrogate endpoint analysis). The patient will be contacted at least 1 week before each visit to be reminded of procedures and investigational product (IP) return.

If the patient is eligible, the Investigator will register the patient for randomization in the IXRS, prior to any other study procedures. If the system confirms the randomization, it will provide the Investigator with a treatment number for the patient.

The following will be performed only at V1:

- Check inclusion/exclusion criteria (detailed in Section 4).
- Randomization to one of 2 treatments groups (elafibranor or placebo in 2:1 ratio, detailed in Section 3.2) via the IXRS.

3.7.2. First Treatment Period visits V1 to V7 (Week 0 to Week 72):

The following procedures will be performed at each of the 12-week visits from V1 to V7:

- IXRS registration
- Physical examination (described in Section 6.2.1)
- Record vital signs and weight (described in Section 6.2.1 and Section 6.2.3)
- Confirmation of adequate diet and lifestyle compliance (described in Section 5.1.1 and APPENDIX II: Adequate diet and lifestyle recommendations), alcohol restrictions (described in Section 5.1.2), and tobacco habits
- Check concomitant/prior medication (described in Section 7.12 and APPENDIX III: Permitted/non-permitted medication)
- Quality of life assessment (V1, V3, V5, and V7, only; described in Section 6.2.6)
- Check AEs (all visits) and occurrence of any clinical outcome (from V2 onwards) (described in

Section 6 and Section 8)
- Study placebo or drug dispensation (described in Section 7.6)
- Blood samples (described in Table 2)
- Plasma & serum bank samples (only if additional genetic and biomarker ICF signed)
- Urinalysis and urinary dipstick (described in Table 2)
- Urinary pregnancy test (for WOCBP only)
- Provision of home pregnancy test kits (for WOCBP only)
- Record result of home pregnancy tests (to be performed every 4 weeks [see Figure 2]) since previous visit (for WOCBP only, every visit from V1)
- Record waist circumference (V1, V3, V5, and V7, only)
- 12-lead ECG (V1, V4, and V7, only; described in Section 6.2.4)
- FibroScan (V1 and V7 only, described in Section 6.2.5)
- Drug accountability (every visit from V2).

Additional procedures to be performed at V7 are:

- Liver biopsy (described in Section 6.1.1). **Note:** the liver biopsy may be performed at V7 or during a separate visit that occurs within the V7 window of 72 weeks ± 1 week from V1. Liver biopsy samples will be sent for central histological evaluation.
- Blood samples for coagulation taken (platelets count and prothrombin time [PT (INR)]; described in Table 2) and tested at a local laboratory prior to the liver biopsy.

3.8. LONG-TERM TREATMENT PERIOD

The main objective to be evaluated during the LTTP will be the prevention of progression to cirrhosis, death due to any cause, or to portal hypertension/cirrhosis related events (as described in Section 1.9.2).

After the 72-week biopsy, patients will continue in the double-blind LTTP, receiving the same treatment as assigned at V1 (elafibranor 120 mg or placebo). Patients will be monitored by notably measuring the appearance of cirrhosis (based on FibroScan measurement associated with biological and/or clinical assessments and confirmed by biopsy).

At or after the 72-week biopsy, a diagnosis of any event listed in the primary composite endpoint described in Section 1.9.2 will result in the permanent discontinuation of study drug and discontinuation of the study following the EOT Visit (as described in Section 3.9 and Section 5.2.3).

3.8.1. Long-term Treatment Period visits (V8 to Vn)

Patients will return to the site every 24 weeks during the LTTP. The patient will be contacted at least 1 week before each visit to be reminded of procedures and IP return.

The following procedures will be performed at each visit from V8 to Vn:

- IXRS registration

- Physical examination (described in Section 6.2.1)
- Record vital signs and weight (described in Section 6.2.1 and Section 6.2.3)
- Confirmation of adequate diet and lifestyle compliance (described in Section 5.1.1 and APPENDIX II: Adequate diet and lifestyle recommendations), alcohol restrictions (described in Section 5.1.2), and tobacco habits
- Check concomitant/prior medication (described in Section 7.12 and APPENDIX III: Permitted/non-permitted medication)
- Quality of life assessment (V8, V9, V11, and every 48 weeks thereafter Section 6.2.6)
- Check AEs and occurrence of any clinical outcome (described in Section 6 and Section 8)
- Study placebo or drug dispensation (described in Section 7.6)
- Blood samples (described in Table 2)
- Plasma & serum bank samples (only if additional genetic and biomarker ICF informed consent signed)
- Urinalysis and urinary dipstick (described in Table 2)
- Urinary pregnancy test (for WOCBP only)
- Provision of home pregnancy test kits (for WOCBP only)
- Record result of home pregnancy tests (to be performed every 4 weeks [see Figure 2]) since previous visit (for WOCBP only, every visit from V1)
- Record waist circumference
- 12-lead ECG (every 48 weeks from V9; described in Section 6.2.4)
- FibroScan (described in Section 6.2.5)
- Drug accountability
- Liver biopsy (at approximately 4 years [V13], and in case of suspected liver cirrhosis, described in Section 6.1.1). Liver biopsy samples will be sent for central histological evaluation
- Blood samples for coagulation taken (platelets count and PT [INR]; described in Table 2) and tested at a local laboratory prior to the liver biopsy.

3.8.2. Long-term Treatment Period phone visits (PV1 to PVn)

Phone visits will be scheduled every 24 weeks starting 12 weeks after Visit 7 for data collection on diet and lifestyle, concomitant medications, clinical outcomes, safety, home pregnancy test results, and IP compliance control. If any information during this phone contact requires a visit, the Investigator may decide to perform an unscheduled visit (described in Section 3.11.2). IXRS registration will be performed for each phone visit.

3.9. END OF STUDY TREATMENT VISIT

At the EOS (upon occurrence of the expected number of events), all patients will be asked to stop treatment and undergo an EOT Visit 30 days after the final administration of study drug.

All patients who permanently discontinue their study medication will undergo an EOT Visit 30 days after the final administration of study drug. Patients who permanently discontinue study drug for any reason

other than an event listed in the primary composite endpoint for long-term efficacy described in Section 1.9.2 will remain, upon agreement, in the study after the EOT Visit and be followed up to evaluate efficacy outcomes and safety through phone call visits every 24 weeks as described in Section 3.10 and Section 5.2.

If a patient discontinues from the study, every attempt should be made to have the patient return to the site and complete the EOT Visit 30 days after the final administration of study drug. For details of the EOT Visit see Table 1, Table 2, Figure 1, and Figure 2.

The patient will be contacted at least 1 week before the visit to be reminded of procedures and IP return (if required). The following procedures will be performed at the EOT Visit:

- IXRS registration
- Physical examination (described in Section 6.2.1)
- Record vital signs and weight (described in Section 6.2.1 and Section 6.2.3)
- Confirmation of adequate diet and lifestyle compliance (described in Section 5.1.1 and APPENDIX II: Adequate diet and lifestyle recommendations), alcohol restrictions (described in Section 5.1.2), and tobacco habits
- Check concomitant/prior medication (described in Section 7.12 and APPENDIX III: Permitted/non-permitted medication)
- Quality of life assessment (described in Section 6.2.6)
- Check AEs and occurrence of any clinical outcome(described in Section 6 and Section 8)
- Blood samples (described in Table 2)
- Plasma & serum bank samples (only if additional genetic and biomarker ICF informed consent signed)
- Urinalysis and urinary dipstick (described in Table 2),
- Urinary pregnancy test (for WOCBP only)
- Record results of home pregnancy tests (to be performed every 4 weeks [see Figure 2]) since previous visit (for WOCBP only)
- Record waist circumference
- 12-lead ECG (described in Section 6.2.4)
- Drug accountability.

Patients discontinuing study drug or discontinuing the study will be asked to return all used and unused study treatments at the EOT Visit.

3.10. FOLLOW-UP FOR PATIENTS WHO HAVE PERMANENTLY DISCONTINUED STUDY DRUG

Patients who have permanently discontinued study drug due to an event listed in the primary composite endpoint for long-term efficacy described in Section 1.9.2 will be discontinued from the study following the EOT Visit and have no further follow-up, unless the patient experiences at the time of EOT visit, an ongoing adverse event possibly related to study treatment for which the follow-up should last until resolution of this adverse event.

Patients who have permanently discontinued study drug for any other reason will remain, upon agreement, in the study and will be followed up with phone visits every 24 weeks (±2 weeks from EOT Visit) following the EOT Visit to report safety, diagnosis of cirrhosis and occurrence of clinical outcomes (as listed below) including liver and cardiovascular events until EOS or the occurrence of an event listed in the primary composite endpoint for long-term efficacy (described in Section 1.9.2), whichever is sooner.

The following procedures will be performed during the follow-up phone visit for patients who have permanently discontinued study drug:

- IXRS registration.
- Reporting of safety information regarding:
  - any new AEs
  - resolution of previous AEs
  - change in severity of existing AEs
  - occurrence of any cardiovascular events
  - occurrence of diabetes (for patients not previously diagnosed with diabetes)
  - worsening of diabetes (for patients previously diagnosed with diabetes).
- Reporting of any change in diet and life style factors
- Reporting of any change (quantitative or qualitative) in therapies post study drug discontinuation
- Reporting of cirrhosis diagnosis (patient to be asked if they have had any histological confirmation of cirrhosis)
- Reporting of any of the following events (primary composite endpoint for long-term efficacy evaluation):
  - liver transplantation
  - MELD score ≥15 for patients with baseline MELD score ≤12
  - the onset of:
    - variceal bleed requiring hospitalization
    - hepatic encephalopathy defined as West Haven/Conn score ≥2 and requiring hospitalization
    - spontaneous bacterial peritonitis
    - ascites requiring treatment.
  - death due to any cause.

3.11. OPTIONAL VISITS

3.11.1. Retesting screening visits

Upon receipt of results from biological assessment done at SV1, and in case a retesting or additional testing is needed according to the selection criteria, an additional visit will be scheduled according to the recommended timeframe for retesting.

Permitted retesting or additional testing in case of abnormal value at SV1 are:

- CPK: can be repeated prior to Randomization (V1) within 1 to 2 weeks after initial test.
- HCV RNA testing: in case positive HVC Ab test at SV1 required latest 2 weeks prior to Randomization (V1).
- HbA1c: can be repeated at the latest 2 weeks prior to Randomization (V1).

Any other retest deemed necessary by the Investigator should be discussed with the Study Medical Monitors.

3.11.2. Unscheduled visits

An unscheduled visit is defined as any visit to the study unit outside of the protocol-evaluation timepoints where the patient is seen by study unit personnel, e.g., when follow-up assessments are required for safety reasons or when repeat measurements are required out of the screening period (either to confirm a measurement or in case of errors, measuring device failure, etc).

Unscheduled visits will be needed for patients who may require further follow-up due to safety.

3.12. OFF-SITE STUDY PROCEDURES IN CASE OF CRISIS SITUATION

Based on assessment of risk, and to ensure patient safety and minimize risks to trial integrity, the sponsor determined that the following optional off-site study procedures can be performed in case a study participant cannot attend an on-site visit during the COVID-19 crisis:

- Safety assessment via phone call
- Local lab assessment
- Delivery of the study treatment to patient
- Visit to patient's home

These options apply to all on-site study visits except for the randomization visit (Visit 1). Visit 1 must occur on-site as per section 3.7.1.

These solutions can be applied depending on the investigator's judgment of each case and the patient's agreement. The alternative solutions can be implemented in response to the COVID-19 crisis prior to the notification or submission to and approval of regulatory agencies and ethics committees.

Before implementing any of these options for a patient, the site will contact the patient to check whether he/she agrees with the off-site procedures.

The patient will be invited to attend an on-site visit to complete the study procedures as per protocol, as soon as the situation allows it.

In cases of any future emergency (e.g., pandemic, political strife, natural disasters), to continue to ensure patient safety and minimize risks to trial integrity, after completion of a risk assessment similar measures could be taken.

3.12.1. Safety and drug compliance procedures

The following procedures will be performed via either a phone contact, or, if safe and possible, a direct visit to the patient:

- Check for AEs and occurrence of any clinical outcome (described in Section 6 and Section 8)
- Report any change in diet and life style factors
- Check concomitant/prior medication (described in Section 7.12 and APPENDIX III: Permitted/non-permitted medication)
- Record result of home pregnancy tests (to be performed every 4 weeks [see Figure 2]) since previous visit (for WOCBP only, every visit from V1)
- Drug accountability
    - dates of any study drug interruption since the last dispensation and reason*
    - end of treatment (if applicable): date of last dose of study drug and reason*
    - end of study (if applicable) : date of end of study and reason*
- if the reason is related to an AE, collect all required details
- Physical examination if possible with a direct visit to the patient (described in Section 6.2.1)
- Record vital signs and weight if possible with a direct visit to the patient (described in Section 6.2.1 and Section 6.2.3)
- Based on the study visit period for the patient, excluding the quality of life assessment, additional protocol related procedures of Section 3.7.2 or Section 3.8.1 may be performed if possible and if necessary conditions are met

3.12.2. Local lab assessment

The patient will be asked if he/she can access a local lab in the few days after the phone contact to obtain hematology, biochemistry and urinalysis testing.

If a direct visit to the patient is safe and possible, the appropriate lab parameters corresponding to the on-site study visit as described in Table 2 will be collected.

3.12.3. Delivery of study treatment to the patient

The IXRS registration will be completed to trigger study drug kit assignments, and the assigned drug kits can be shipped to the patient, or delivered directly to the patient by the site study staff if safe and possible.

As per the usual study visit, the patient will be instructed to continue taking the available tablets from the existing kit until he/she receives the new kit.

The study drug compliance and study drug accountability will be performed as described in Section 7.10 and Section 7.11 once brought to the study site/study pharmacy.

3.12.4. Completion of Missed Study Procedures

As soon as the situation allows it, the site will schedule the patient's on-site visit to complete the missed study procedures (those that could not be performed during the phone calls/visit to patient) as per protocol (see Section 3.7.2 or Section 3.8.1).

3.13. EXPLORATORY/ANCILLARY SUBSTUDY

Exploratory substudies might be performed during the study in sites that have the corresponding capability. Specific study documents will be prepared and Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and authority approvals shall be obtained when applicable.

4. PATIENT SELECTION

A patient will be eligible for the study only if all of the following criteria apply:

4.1. INCLUSION CRITERIA

Patients must meet all of the following inclusion criteria to be eligible for enrollment in the trial:

1. Males or females aged from 18 to 75 years inclusive at first Screening Visit.
2. Must provide signed written informed consent and agree to comply with the study protocol.
3. Females participating in this study must be of nonchildbearing potential or using highly efficient contraception for the full duration of the study and for 1 month after the end of treatment, as described below:
    - Cessation of menses for at least 12 months due to ovarian failure,
    - Surgical sterilization such as bilateral oopherectomy, hysterectomy, or medically documented ovarian failure
    - If requested by local IRB regulations and/or National laws, sexual abstinence may be considered adequate (the reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient)
    - Using a highly effective nonhormonal method of contraception (bilateral tubal occlusion, vasectomized partner, or intra-uterine device)
    - Double contraception with barrier AND highly effective hormonal method of contraception (oral, intravaginal, or transdermal combined estrogen and progestogen hormonal contraception associated with inhibition of ovulation; oral, injectable, or implantable progestogen-only hormonal contraception associated with inhibition of ovulation; or intrauterine hormone-releasing system). The hormonal contraception must be started at least 1 month prior to Randomization.
4. Histological confirmation of steatohepatitis on a diagnostic liver biopsy by central reading of the slides (biopsy obtained within 6 months prior to Screening or during the Screening Period) with at least 1 in each component of the NAS (steatosis scored 0-3, ballooning degeneration scored 0-2, and lobular inflammation scored 0-3).
5. NAS ≥4.
6. Fibrosis stage of 1 or greater and below 4, according to the NASH CRN fibrosis staging system.
   For patients with fibrosis stage 1, only patients at high risk of progression will be included meaning with a NAS ≥5 and at least 2 of the following conditions: persistent elevated ALT (absence of normal ALT within the past year), obesity defined by a BMI ≥30, metabolic syndrome (NCEP ATP III definition), type 2 diabetes, or HOMA-IR >6.
7. Patients in whom it is safe and practical to proceed with a liver biopsy, and who agree to have:

- 1 liver biopsy during the Screening Period for diagnostic purpose (if no historical biopsy within 6 months before screening is available)
- 1 liver biopsy after 72-weeks of treatment for assessment of the treatment effects on NASH
- a final liver biopsy after approximately 4 years of treatment (V13), unless a liver biopsy has already been performed within the past year
- 1 liver biopsy performed only in the case of suspicion of cirrhosis (to have a histological confirmation.

8. If a patient is treated with 1 of the following drugs: vitamin E (>400 IU/day), polyunsaturated fatty acids (>2 g/day), or UDCA; a stable dose from at least 6 months prior to diagnostic liver biopsy is required.
9. For patients with type 2 diabetes, glycemia must be controlled. If glycemia is controlled by antidiabetic drugs, change in anti-diabetic therapy must follow these requirements:
    - no qualitative change 6 months prior to diagnostic liver biopsy up to Randomization (i.e., implementation of a new anti-diabetic therapy) for patients treated with metformin, gliptins, sulfonylureas, sodium/glucose cotransporter (SGLT) 2 inhibitors, glucagon-like peptide (GLP)-1 agonists, or insulin. Dose changes of these medications are allowed in the 6 months prior to diagnostic liver biopsy, except for GLP-1 agonists, which must remain on stable dose in the 6 months prior to diagnostic liver biopsy.
    - no implementation of GLP-1 agonists and SGLT2 inhibitors up to 72 weeks of treatment (V7).

    Initiation of any other antidiabetic drugs is allowed after Randomization based on treating physicians' judgment, except for glitazones which are prohibited 6 months prior to diagnostic liver biopsy until the end of treatment.

4.2. EXCLUSION CRITERIA

Patients who meet any of the following criteria will be excluded from entering the study:

1. Known chronic heart failure (Grade I to IV of New York Heart Association classification).
2. History of efficient bariatric surgery within 5 years prior to Screening, or planned bariatric surgery in the course of the study.
3. Uncontrolled hypertension during the Screening Period despite optimal antihypertensive therapy.
4. Type 1 diabetes patients.
5. Patients with HbA1c >9.0%. If abnormal at the first Screening Visit, the HbA1c measurement can be repeated at the latest 2 weeks prior to Randomization. A repeated abnormal HbA1c (HbA1c >9.0%) leads to exclusion.
6. Patients receiving thiazoledinediones (glitazones [pioglitazone, rosiglitazone]), unless the drug was discontinued at least 6 months before the diagnostic liver biopsy.

7. Patients with a history of clinically significant acute cardiac event within 6 months prior to Screening such as: stroke, transient ischemic attack, or coronary heart disease (angina pectoris, myocardial infarction, revascularization procedures).
8. Weight loss of more than 5% within 6 months prior to Randomization.
9. Compensated and decompensated cirrhosis (clinical and/or histological evidence of cirrhosis). Notably, NASH patients with fibrosis stage = 4 according to the NASH CRN fibrosis staging system are excluded.
10. Current or recent history (<5 years) of significant alcohol consumption. For men, significant consumption is typically defined as higher than 30 g pure alcohol per day. For women, it is typically defined as higher than 20 g pure alcohol per day. See APPENDIX IV: Alcohol comparison table.
11. Pregnant or lactating females or females planning to become pregnant during the study period.
12. Other well documented causes of chronic liver disease according to standard diagnostic procedures including, but not restricted to:
    - Positive hepatitis B surface antigen (HBsAg)
    - Positive HCV RNA, (tested for in case of known cured HCV infection, or positive HCV Ab at Screening)
    - Suspicion of drug-induced liver disease
    - Alcoholic liver disease
    - Autoimmune hepatitis
    - Wilson's disease
    - Primary biliary cirrhosis, primary sclerosing cholangitis
    - Genetic homozygous hemochromatosis
    - Known or suspected HCC
    - History or planned liver transplant, or current MELD score >12.
13. Where applicable, patients not covered by Health Insurance System and/or not in compliance with the recommendations of National Law in force applicable to clinical trials.
14. Patients who cannot be contacted in case of emergency.
15. Known hypersensitivity to the investigation product or any of its formulation excipients.
16. Patients with previous exposure to elafibranor.
17. Patients who are currently participating in, plan to participate in, or have participated in an investigational drug trial or medical device trial containing active substance within 30 days or five half-lives, whichever is longer, prior to Screening.

Concomitant medications (see APPENDIX III: Permitted/non-permitted medication):

18. Fibrates are not permitted from 2 months before Randomization. Patients that used statins, ezetimibe, or nonfibrate lipid lowering drugs before Screening may participate if the dosage has been kept constant for at least 2 months prior to Screening.
19. Currently taking drugs that can induce steatosis/steatohepatitis including, but not restricted to: corticosteroids (parenteral & oral chronic administration only), amiodarone (Cordarone), tamoxifen

(Nolvadex), and methotrexate (Rheumatrex, Trexall), which are not permitted 30 days prior to Screening and up to end of treatment.

20. Currently taking any medication that could interfere with study medication absorption, distribution, metabolism, or excretion or could lead to induction or inhibition of microsomal enzymes, e.g., indomethacin, which are not permitted from Randomization until end of treatment.

Associated illnesses or conditions:

21. Any medical conditions that may diminish life expectancy to less than 2 years including known cancers.
22. Evidence of any other unstable or, untreated clinically significant immunological, endocrine, hematological, gastrointestinal, neurological, neoplastic, or psychiatric disease
23. Mental instability or incompetence, such that the validity of informed consent or ability to be compliant with the study is uncertain.

In addition to the above criteria, patient should not present any of the following biological exclusion criteria:

24. Positive anti-human immunodeficiency virus (HIV) antibody.
25. AST and/or ALT >10 x upper limit of normal (ULN).
26. Conjugated bilirubin >1.50 mg/dL due to altered hepatic function. Note: Gilbert Disease patients are allowed into the study.
27. INR >1.40 due to altered hepatic function.
28. Platelet count <100,000/mm3 due to portal hypertension.
29. Serum creatinine levels >1.53 mg/dL in males and >1.24 mg/dL in females.
30. Significant renal disease, including nephritic syndrome, chronic kidney disease (defined as patients with markers of kidney damage or eGFR of less than 60 ml/min/1.73 m2).
31. Unexplained serum CPK >3 x the ULN. In case of explained elevated CPK >3 x the ULN, the measurement can be repeated prior to Randomization. In this case, retest should be performed within 1 to 2 weeks after initial test. A CPK retest >3 x ULN leads to exclusion.

5. TRIAL PROCEDURES

The procedures performed at each visit are summarized in the study schedules (see Table 1, Table 2, Figure 1, and Figure 2) and in Section 3.

The Investigator will be asked, whenever possible, to schedule patient visits at the same time of day for each patient. A patient may be seen at any time for reasons of safety.

During each visit, lifestyle and study recommendations will be repeated, vital signs will be measured, and the patient will be queried in the form of an open question regarding new or continuing events.

Procedures for premature discontinuation after SV1 are described in Section 5.2.

5.1. LIFESTYLE RECOMMENDATIONS AND STUDY RECOMMENDATIONS

5.1.1. Standard diet and exercise recommendations

Standard diet and exercise recommendations given by the Investigator during SV1 will be given at the beginning of each patient's participation and will be maintained throughout the study. These recommendations will be based on Therapeutic Lifestyle Change (TLC) counseling (or local equivalent) according to NCEP ATP III guidelines. The essential components of TLC and the macronutrient recommendations for the TLC diet are detailed in APPENDIX II: Adequate diet and lifestyle recommendations.

Assessment of dietary and lifestyle compliance will occur at each visit by asking the patient 2 questions to confirm if they have remained compliant to the diet and lifestyle recommendations. A yes/no response will be recorded in the electronic care report form (eCRF).

5.1.2. Dietary, fluid, and lifestyle restrictions

The following restrictions should be applied to patients in this trial from SV1 through to the end of the study:

- Patients will be required to fast (no food or drink other than water) for at least 12 hours prior to all blood sampling. As such, patients should not consume any breakfast or take any medication (including study medication) in the morning prior the blood sampling. In case the patients do not fast before a visit, a new appointment will be scheduled within 7 days.
- On each study visit day, study treatment will be taken under fasting conditions after the blood sampling (which corresponds to the day of the visit).
- During the 48 hours preceding each study visit, patients should not perform strenuous exercise.
- Patients are to avoid consumption of dietary supplements such as anti-oxidant (including, but not limited to Vitamin A, Vitamin C, provitamin A, selenium, and polyphenol).
- Alcohol consumption should be limited during the study duration and registered in the eCRF. Alcohol consumption of more than 20 g per day for women and 30 g per day for men is considered abusive

(see APPENDIX IV: Alcohol comparison table). A standard drink is equal to 14.0 grams (0.6 ounces) of pure alcohol. Generally, this amount of pure alcohol is found in:

- 12-ounces/350 ml of beer (5% alcohol content)
- 5-ounces/150 ml of wine (12% alcohol content)
- 1.5-ounces/50 ml (40% alcohol content) distilled spirits or liquor (e.g., gin, rum, vodka, whiskey).

Concomitant therapy is restricted and any change to treatment or introduction of a new treatment should be discussed with the Investigator before doing so (see Section 7.12 and APPENDIX III: Permitted/non-permitted medication).

5.1.3. Home pregnancy test for women of childbearing potential

Women of childbearing potential are required to perform a pregnancy test every 4 weeks. Home pregnancy test kits will be supplied at each visit to WOCBP and these are to be performed as per the kit instructions every 4 weeks between study visits. Negative results are to be reported at the next scheduled visit or telephone visit (see Table 1 and Figure 2). In the event of a positive result the patient must discontinue study drug immediately and report the result to the Investigator as soon as possible (see Section 8.6.1).

5.1.4. Sun exposure

As a conservative approach patients will be advised to avoid extended ultra-violet light exposure without protection from V1 through to the end of the study (see Section 1.4.4.4).

5.2. PATIENT WITHDRAWAL AND PATIENT TREATMENT DISCONTINUATION RULES

5.2.1. Handling of patient withdrawal

Patients will be informed that they have the right to discontinue the study at any time, for any reason, without affecting future management and treatment.

5.2.2. Permanent discontinuations of study drug

In some instances, it may be necessary for a patient to permanently discontinue study drug. The patient may be discontinued from study drug at any time at the discretion of the Investigator or Sponsor for safety, behavioral, or administrative reasons. In keeping with the ITT analysis, the patient will not be permanently discontinued from the study.

The reason for permanent discontinuation of study drug should be documented in the eCRF and the Medical Monitor informed. If the discontinuation of study drug is due to an AE, the event should be documented in the eCRF.

Some possible reasons that may lead to permanent early study drug discontinuation include:

- Occurrence of any event listed in the composite endpoints for long-term efficacy evaluation (see

Section 1.9.2)

- In the opinion of the Investigator, any AE, SAE (described in Section 8), or significant change in a laboratory value that warrants permanent discontinuation of study drug therapy. Investigators are advised to call the Medical Monitor prior to making such a decision
- Occurrence of repeated hypoglycemic episodes without possibility for a down titration of background therapy that may put the patient at risk with continued participation
- Non-permitted concomitant medication (described in Section 7.12 and APPENDIX III: Permitted/non-permitted medication)
- Female patients who are pregnant (see Section 8.6.1) or are breastfeeding or who do not agree to use a reliable method of birth control during the study will be permanently discontinued from study drug
- Non-compliance with the study treatment
- Uncooperative patient
- The patient requests to stop study drug permanently.

Patients permanently discontinued from study drug will be requested to stop taking study drug and attend an EOT Visit 30 days after the last administration of study drug (described in Section 3.9).

If the study drug is discontinued due to the occurrence of any event listed in the composite endpoints for long-term efficacy evaluation (see Section 1.9.2), the patient will also be discontinued from the study with no further follow-up after the EOT Visit, unless the patient experiences at the time of EOT visit, an ongoing adverse event possibly related to study treatment for which the follow-up should last until resolution of this adverse event.

If the study drug is discontinued due to any reason other than the occurrence of any event listed in the composite endpoints for long-term efficacy evaluation, the patient will undergo, if agreed, telephone visits every 24 weeks (described in Section 3.10) after the EOT Visit until the EOS or the occurrence of any event listed in the primary composite endpoints for long-term efficacy evaluation (see Section 1.9.2), whichever is sooner.

5.2.3. Patient discontinuation from the Study

Patient discontinuation prior to the patient's completion of the study is expected to be low, occurring if the patient withdraws consent, or if enrollment in any other clinical trial involving an investigational product, or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study, occurs.

At the time of discontinuing from the study, the Medical Monitor and IXRS should be contacted, and, if possible, an EOT Visit should be conducted (see Section 3.9). The patient will be permanently discontinued from the study at that time with no further follow-up and the date the patient is withdrawn from the study and the reason for withdrawal should be appropriately documented in the eCRF. During the study close-out period, survival status will be collected within legal and ethical boundaries for all patients randomized who

withdrew participation from the study.

Where possible, patients withdrawn from the study will be followed until resolution of all their SAEs or possibly related AEs until the unresolved SAEs or possibly related AEs are judged by the Investigator to have stabilized.

5.2.4. Patients lost to follow-Up

A patient would be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. Site personnel are expected to make diligent attempts to contact patients who fail to return for a scheduled visit or were otherwise unable to be followed up by the site. Vital status will be collected within legal and ethical boundaries for all patients randomized, including those who did not get study drug. Vital status will be searched in public sources during the study close-out period. If vital status is determined, the patient will not be considered lost to follow-up.

5.2.5. Replacement

No patient replacements are permitted in this study.

5.2.6. Premature discontinuation of the study

Premature termination of this clinical trial may occur because of a Regulatory Authority decision, change in opinion of the IRB/IEC, drug safety problems, DSMB recommendations, or at the discretion of the Sponsor. In addition, the Sponsor retains the right to discontinue development of the study treatment at any time.

The Sponsor reserves the right to discontinue the trial prior to inclusion of the intended number of patients, but intends only to exercise this right for valid scientific or administrative reasons. After such a decision, the Investigator must contact all participating patients within a reasonable period of time. As directed by the Sponsor, all trial materials must be collected and all eCRFs completed to the greatest extent possible.

Furthermore, the Investigator can decide to prematurely discontinue the study. In that event, the Investigator must notify the Sponsor immediately of his/her decision and give the reason in writing. Prompt compliance with this requirement is essential so that the Sponsor may comply with its regulatory obligations.

In all cases, ethics committee (IRB/IEC) and Health Authorities should be informed.

If the Investigator decides to prematurely discontinue the study, all test articles, eCRFs, and related study materials must be returned to the Sponsor.

5.3. PATIENT RESCREENING

Re-screening is allowed in a screen failed patient if there is a change in the situation of the patient which allows him/her to fulfill inclusion/exclusion criteria. This will need sponsor approval. In case of re-

screening the patient will need to sign a new informed consent and will be entered as a new patient, with a new patient number.

6. ASSESSMENTS

6.1. EFFICACY AND SAFETY ASSESSMENTS

6.1.1. Histological assessments

A liver biopsy (see Section 6.1.1.1 for recommendations) will be performed:

- At baseline
- After 72 weeks of treatment
- After approximately 4 years of treatment (V13) unless a biopsy has been performed within the previous year.
- In the case cirrhosis is suspected at any interim visit during the LTPP (based on FibroScan and/or clinical and biological assessments)

A Laboratory Manual will be provided to each trial site. The manual will outline the collection process, and shipping requirements for the specific central laboratory.

6.1.1.1 Recommendations related to liver biopsy

Before performing a percutaneous liver biopsy, there must be a clearly defined indication for the biopsy, and the risks to the patient should not outweigh the potential benefits. This will be assessed by the investigator according to local practice.

The patient's platelet count and PT should be checked according to local hospital standards before the date of liver biopsy. Local guidelines and thresholds for hemostatic parameters should be used as they are in everyday clinical practice. Usually a platelet count >80,000/mm^3, a PT >60% or longer by no more than 4 seconds over the control, and a normal bleeding time are acceptable for performing percutaneous liver biopsy in a patient that has stopped taking any antiaggregant therapy for >5 days. If these conditions are not all respected, a safer option would be to perform the liver biopsy by transjugular route, when available.

Sedation is recommended to be given for percutaneous liver biopsy, and should be given with caution in liver disease.

The recommended biopsy procedure to be applied is:

- Needle core biopsy
- Biopsy obtained with a 16 or lower gauge needle
- A tissue core ≥2 cm long (≥10 portal tracts) represents optimal biopsy length
- Preferably obtain biopsy from the right lobe. If left lobe biopsy is used for inclusion, a left lobe biopsy should be used for future biopsies.

Post-biopsy observation: It is recommended that the patient should remain in hospital at least for 6 hours after the procedure.

The biopsies will be sent to the central laboratory and then to a central reader who will read the biopsies to determine the eligibility to the study according the fibrosis stage and consistency with NASH diagnosis. Biopsy slides will be blinded for patient and visit identification prior to central reading.

In case the liver biopsy fragment is too small or of bad quality, thereby precluding adequate reading, other available slides or new slides to be prepared from an available block of tissue may be requested to the site.

6.1.1.2 Liver biopsy reading for NAS and NASH CRN fibrosis score

Histological changes from baseline to Week 72 and any follow-up biopsy will be evaluated. Liver biopsy samples will be sent to the central pathology laboratory (Liverpat, 28 rue de l'amiral Hamelin, 75 116 Paris–France) where they will be read and scored. Scores for total NAS, steatosis, ballooning, lobular inflammation, or portal inflammation, as well as fibrosis scores (both by NASH CRN scoring system, and NAFLD Ishak scoring system) and fibrosis area by morphometry will be evaluated.

6.1.2. Biological assessments

All blood samples for efficacy and/or for safety assessment (as described in Table 2) will be returned and centralized by the central laboratory (Cerba Research: Ghent – Belgium, New York – USA, Sydney – Australia, or BARC: Johannesburg – South Africa) and specific analyses will be performed by another laboratory (GENFIT- Loos, France).

A laboratory manual will be provided to each trial site.

The manual will outline the collection process and shipping requirements for the specific central laboratory. Blood sampling will be performed by trained personnel at each site. Blood samples will be processed and shipped as outlined in the laboratory manual. Refer to the laboratory manual for exact amounts of blood required for each test.

For all visits, reportable laboratory results (except serology) will be available at sites approximately 24 hours after receipt of samples. Final results will be sent to sites. Laboratory reports should be reviewed, signed, and dated by the Investigator as soon as they are received. The Investigator should comment upon out of range parameters and assess clinical significance.

The option to retest during the study is left to the Investigator's judgment. During Screening, retesting (to be performed at retesting screening visits) is limited to HbA1c, CPK, and HCV RNA, as described Section 3.11. Any other retest deemed necessary by the Investigator should be discussed with the Study Medical Monitors.

In case the lab sampling may not be performed at the scheduled visit, patients should come back to the site within 7 days of the visit for lab sampling.

6.1.2.1 Laboratory assessments

Clinical laboratory evaluations (including hematology, blood chemistry, and urinalysis) will be measured at every visit as described in Table 2.

Hematology and urinalysis (dipstick) will be measured at all visits. Both blood and urine sample will be transported to the central laboratory for testing and analysis. At Screening, the Screening Visit 1 chemistry panel will be measured.

The V1 to Vn total chemistry panel and urine analysis will be measured at all visits from V1 to EOT visits. It is recommended to collect first morning urine samples for urinalysis.

6.1.2.2 Urinary pregnancy tests

Urinary pregnancy tests will be supplied to each site to perform a pregnancy diagnostic at each visit during the study on WOCBP. These tests will also be given to the WOCBP to perform a pregnancy test at home every 4 weeks in between visits (see Section 5.1.3).

6.1.2.3 Serology (SB1)

Screens for a hepatitis panel and HIV antibodies will be performed at SV1:

- HIV ab I/II
- HBsAg
- HCV ab (in case of known cured HCV infection, HCV RNA can be tested directly at SV1; otherwise, HCV RNA should be tested at a Retesting Screening Visit, only in case HCV ab>0 at SV1 [see Section 3.11.1])

6.1.2.4 Other parameters

Liver markers, calculated fibrosis and steatosis index, safety, and inflammatory markers, as well as special glycemic and lipid parameters, will be measured at V1, V3, V5, and V7 during the First Treatment Period, at each visit during LTTP, and at the EOT visit. CHI3L1 will only be tested at V1, V7, and V13 (at the time of the approximate 4 year biopsy).

6.1.3. Constitution of biobank

In order to be able to test other specific parameters which could be of interest regarding the elafibranor development program or regarding diagnosis, prevention, or treatment of NASH or other related diseases, an additional amount of serum & plasma will be kept at each visit (including screening visits) from patients who have given their consent for these additional analyses by signature of the genetic and biomarker ICF.

These samples will be used:

- To discover or validate biomarkers in NASH and related diseases.
- To investigate the role of selected single nucleotide polymorphisms in the response to treatment.

These samples will be destroyed 3 years after study results at the latest.

6.2. OTHER SAFETY ASSESSMENTS AND ONGOING SAFETY MONITORING

6.2.1. Physical examination

A physical examination will be performed and weight measured at each visit (with the exception of the potential SV2). Height will be measured at SV1 only.

The patient's weight will be measured under the same conditions at each visit. Where possible, the scale for weight must be the same for a given patient throughout the visits.

6.2.2. Waist circumference

Waist circumference will be measured at the midpoint between the lateral iliac crest and the lowest rib in cm during expiration. The measuring tape should be snug but not compressing the skin and held parallel to the floor. The measurement is to be made at normal respiration.

6.2.3. Vital signs

Blood pressure (mmHg) and pulse rate (beats per minute) will be measured at each visit (with the exception of the potential SV2 visit) according to the "Recommendations for Blood Pressure Measurement in Humans and Experimental Animals" published in an American Heart Association scientific statement.

6.2.3.1 Important points for clinical blood pressure measurement

- The patient should be seated comfortably with the back supported and the upper arm bare without constrictive clothing. The legs should not be crossed.
- The arm should be supported at heart level, and the bladder of the cuff should encircle at least 80% of the arm circumference.
- When using a mercury sphygmomanometer, the mercury should be deflated at 2 to 3 mm/s, and the first and last audible sounds should be taken as systolic and diastolic pressure. The column should be read to the nearest 2 mmHg.
- Neither the patient nor the observer should talk during the measurement.

Systolic BP and diastolic BP will be measured after 5 minutes rest in the seating position with a standard mercury sphygmomanometer or a validated sphygmomanometer. Where possible, the validated manometer should be the same for a given patient throughout the visits.

6.2.4. Electrocardiogram

A standard 12-lead ECG will be obtained at V1, V4, and V7 in the First Treatment Period, every 48 weeks in the LTTP starting at V9, and at the EOT visit.

Electrocardiograms will be recorded using 12-lead ECG recorders following 10 minutes rest in the supine position. A minimum of 3 cycles will be recorded per lead.

The ECGs will be analyzed by the Investigator. Any potential clinical significance of ECG changes will be determined by the Investigator with relation to the patient's medical history, physical examination, and concomitant medications and recorded in the eCRF.

6.2.5. FibroScan

A FibroScan exam will be performed at V1 and V7 in the First Treatment Period and at each visit in the LTTP. Where possible, FibroScan must be done at the day of visit. Otherwise, it can be performed within 7 days around the visit date.

Recommendations for ensuring a reliable examination are:

- Patient must be fasting for at least 2 hours before the FibroScan examination
- At least 10 consecutive and successful measurements shall be performed without changing probe position
- InterQuartile Range (IQR)/Median stiffness ratio (in %) shall remain <30% at the end of the scan, to consider a FibroScan measure as reliable. If not, it is recommended to perform a few additional individual measures, or to restart the entire FibroScan examination

6.2.6. Quality of life questionnaire

A standardized and validated questionnaire for quality of life (SF-36) will be completed by patients at V1, V3, V5, and V7 in the First Treatment Period, and V8, V9, V11, and every 48 weeks thereafter in the LTTP until, and including the EOT visit.

6.3. IMPORTANT SPECIFIC BIOLOGICAL CONSIDERATIONS AND PATIENT DISCONTINUATION RULES

6.3.1. Creatine phosphokinase

If at any visit during the treatment periods, a patient experiences diffuse myalgia, muscle tenderness, and/or marked increase in muscle CPK values (≥3 x ULN and ≤5 x ULN), an additional visit and test within 3 to 7 days must be performed. If, during that visit, the patient still experiences diffuse myalgia, muscle tenderness and/or marked increase in muscle CPK values (≥3 x ULN and ≤5 x ULN), myopathy must be considered and the patient must be discontinued from study treatment immediately and followed up as

described in Section 5.2.2.

If at any visit during the treatment periods, a patient experiences marked increase in muscle CPK values >5 x ULN, unexplained by strenuous exercise or trauma, the patient must be discontinued from study treatment immediately and followed up as described in Section 5.2.2. In case of exercise and/or trauma, the CPK should be repeated once weekly to verify decrease of CPK, until CPK lowers to ≤5 x ULN.

6.3.2. Liver function monitoring

All liver decompensation events included in the composite efficacy endpoint (Section 1.9.2) will be adjudicated by the Clinical Events Committee (CEC; see Section 6.5), as well as all DILI events (see Section 6.5).
Criteria used for reporting a potential DILI for adjudication are given below and correspond to the criteria leading to permanent study drug discontinuation.
For DILI adjudication, assessment may be performed using as baseline either historical AST, ALT, total bilirubin, and INR results meeting the requirements of within 8 weeks to 6 months of planned randomization visit (V1), or, using lab results from SV1 and V1 that are at least 8 weeks apart.

In all cases, whether baseline AT values are normal or elevated, an increase of AT >10 x ULN will lead to permanent discontinuation of the patient from study drug, and scheduling of EOT visit (Section 3.9).

6.3.2.1 Monitoring of patients with normal baseline aminotransferase values

Liver function monitoring requirements for patients with normal baseline AT values at V1 who at any visit from V2 onwards during the treatment periods exhibit:

- Increase in AT to ≤3 x ULN: no additional action required, schedule next visit as per assessment schedule
- Increase in AT to >3 x ULN but ≤5 x ULN: retest after 48 to 72 hours If during the following retest:
  - AT remains >3 x ULN but ≤5 x ULN: continue the drug with close serial monitoring (once a week)
  - AT increases to >5 x ULN: permanently discontinue patient from study drug and schedule EOT Visit (see Section 3.9 and Section 5.2.2).
- Increase in AT >5 x ULN: retest after 48 to 72 hours If during the following retest:
  - AT remains >5 x ULN: permanently discontinue patient from study drug and schedule EOT Visit (see Section 3.9 and Section 5.2.2)
  - AT reduces to ≤5 x ULN: continue the drug with close serial monitoring (once a week).
- Increase in AT >3 x ULN AND increase in total bilirubin >2 ULN: permanently discontinue patient from study drug and schedule EOT Visit (see Section 3.9 and Section 5.2.2).
- Increase in AT >3 x ULN AND increase in INR>1.5 (except in case of anticoagulant therapy): permanently discontinue patient from study drug and schedule EOT Visit (see Section 3.9 and

Section 5.2.2).

- Increase in AT >3 x ULN AND fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash: permanently discontinue patient from study drug and schedule EOT Visit (see Section 3.9 and Section 5.2.2).
- Increase in AT >3 x ULN AND eosinophilia (>5%) with total count > ULN: permanently discontinue patient from study drug and schedule EOT Visit (see Section 3.9 and Section 5.2.2).

6.3.2.2 Monitoring of patients with increased baseline aminotransferase values

Liver function monitoring requirements for patients with increased AT baseline values at V1 who at any visit post V1 onwards during the treatment periods exhibit:

- Increase in AT to ≤3 x baseline value: no additional action required, schedule next visit as per assessment schedule
- Increase in AT to >3 x baseline value but ≤10 x ULN: retest after 48 to 72 hours
    - AT remains >3 x baseline value but ≤10 x ULN: continue the drug with close serial monitoring (once a week)
    - AT increases >5 x baseline value or >10 x ULN: permanently discontinue patient from study drug and schedule EOT Visit (see Section 3.9 and Section 5.2.2).
- Increase in AT >3 x baseline value AND increase in total bilirubin > 2 x ULN: permanently discontinue patient from study drug and schedule EOT Visit (see Section 3.9 and Section 5.2.2).
- Increase in AT >3 x baseline value AND increase in INR>1.5 (except in case of anticoagulant therapy): permanently discontinue patient from study drug and schedule EOT Visit (see Section 3.9 and Section 5.2.2).
- Increase in AT >3 x baseline value AND fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash: permanently discontinue patient from study drug and schedule EOT Visit (see Section 3.9 and Section 5.2.2).
- Increase in AT >3 x baseline value AND eosinophilia (>5%) with total count > ULN: permanently discontinue patient from study drug and schedule EOT Visit (see Section 3.9 and Section 5.2.2).

6.3.3. Threshold for diagnosis of cirrhosis

A FibroScan and serum markers assessments will be performed every 24 weeks at each visit in the LTTP.

A liver biopsy may be considered in order to confirm the diagnosis of cirrhosis if during a LTTP visit the FibroScan value is ≥ 14 kPa (with IQR/Median stiffness ratio < 30%*) associated with a platelet count <150 000/mm^3 and at least 1 elevated serum marker of fibrosis indicative of cirrhosis (calculated NAFLD fibrosis >0.676 score or reported FIB-4 >2.67).

*InterQuartile Range (IQR)/Median stiffness ratio (in %) shall remain <30% at the end of the scan, to consider a FibroScan measure as reliable. If not, it is recommended to perform a few additional individual measures, or to restart the entire FibroScan examination.

In the case of detection of variceal rupture at endoscopy or of presence of any cirrhosis related event, such as MELD ≥15, hepatic encephalopathy, or ascites, then the liver biopsy will not be required for diagnosis of cirrhosis, but the diagnosed event will have to be adjudicated by the CEC.

If cirrhosis or any event listed in the long-term composite endpoint is diagnosed, the patient will discontinue the study drug and the study and will be followed up as described in Section 5.2.2 and Section 5.2.3.

6.4. SAFETY & EFFICACY DATA REVIEW

An independent DSMB will be established in order to review the progress of the study and to perform a safety data review on a regular basis during the trial to protect patient welfare and preserve study integrity. The DSMB will also review the interim analysis results and provide final recommendations regarding trial termination due to futility and adjustment of the target number of primary events. A detailed description of the interim analysis procedures and decision-making process will be provided in the DSMB Charter.

The DSMB will consist of at least 5 experienced physicians (1 endocrinologist, 1 cardiologist, 1 hepatologist, 1 oncologist, and 1 nephrologist) and 1 statistician, all of whom will be independent of the participants in the study. The DSMB Charter will define the role, responsibilities, rules, and tasks of the DSMB.

6.5. CLINICAL EVENT COMMITTEE

The CEC will conduct adjudication of all disease progression events included in the primary composite efficacy long-term endpoint (Section 1.9.2), all DILI events, and all major cardiovascular events as defined in the CEC charter. The CEC assessment and adjudication will occur in a blinded, consistent, and unbiased manner throughout the course of a study to determine whether the endpoints meet the protocol-specified criteria.

The CEC will be comprised of 2 hepatologists, 2 cardiologists, 1 endocrinologist and 3 histopathologists, all of whom will be independent of the participants in the study.

6.6. GUIDANCE FOR INVESTIGATORS

6.6.1. Summary of safety data

The safety and tolerability of elafibranor were confirmed in Phase I and Phase II studies.

A Phase I program to assess the safety and tolerability, as well as the PK profile, of elafibranor has been conducted through 12 completed and 5 ongoing clinical trials. A total of 659 volunteers were randomized in these studies performed in Phase I centers, including 561 healthy lean subjects, 60 overweight or obese

subjects, and 12 patients with type 2 diabetes, 6 with end stage renal disease and 20 with hepatic impairment (Child-Pugh class A, B or C) have been randomized to date in the completed trials. Elafibranor daily doses ranged between 5 mg and 360 mg, with a treatment duration up to 16 days.

A Phase II program was initiated to assess the safety and efficacy profile of elafibranor in patients suffering from cardiometabolic disorders and NASH. To date, 5 Phase IIa studies have been completed in which 297 patients were randomized. A Phase IIb trial has been completed, and evaluated the efficacy and safety of elafibranor 80 mg and 120 mg on steatohepatitis in 274 patients with NASH. A Phase 2 study (GFT505B- 216-1) was also conducted in Primary Biliary Cholangitis (PBC) and included 45 patients with PBC and inadequate response to UDCA. This study evaluated the efficacy and safety of elafibranor at doses of 80 mg and 120 mg after 12 weeks of treatment. In the Phase 2 program, the elafibranor daily doses ranged between 30 mg and 120 mg, with a maximum treatment duration of 12 months.

Of the 63 Treatment emergent SAEs that have been reported cumulatively in the completed clinical development program, 50 occurred with elafibranor and 13 with placebo. For all SAEs, the treatment code has been broken (end of study unblinding).

Of the 50 SAEs that occurred with elafibranor, only 10 SAEs reported in 7 subjects were considered as having a reasonable possibility of relationship to elafibranor by the investigators (serious adverse reaction). They consisted of:

- Atrial fibrillation in a patient with history of arterial hypertension and suspected chronic coronary disease treated with elafibranor 80 mg
- Acute cholecystitis and pancreatitis that occurred in a patient on the second day of drug administration of elafibranor 80 mg
- Spontaneous abortion in a pregnant patient treated for 6 months with elafibranor 80 mg
- Ataxia, tremor and fasciculations in a patient treated for 51 weeks with elafibranor 80 mg
- Acute pancreatitis that occurred after 7 weeks of treatment in a patient treated with elafibranor 120 mg.
- Parkinson's disease in a patient treated for 12 months with elafibranor 120 mg, aged 76 years (in the risk group for Parkinson's disease, and with a family history of Parkinson's disease).
- Autoimmune hepatitis in a 56-year-old subject after 12 weeks of treatment of 120 mg elafibranor. The subject received her last dose of investigational product before the event.

For atrial fibrillation, acute cholecystitis and pancreatitis, and Parkinson's disease, after later investigations, given the medical history of the patients or the time of occurrence of the event, relationship to elafibranor was judged as "no reasonable possibility" by the Sponsor.

All adverse reactions (adverse events reported by investigators as possibly related or related to study drug) reported in more than 1% of patients treated with elafibranor in clinical studies with repeated doses of at least 80 mg elafibranor per day are summarized in Table 3.

Table 3: **Overview of the common nonserious adverse reactions (>1% of patients treated with elafibranor) by system organ class (SOC) reported in completed elafibranor clinical studies with repeated administration of elafibranor (at least 14 days) from 80 mg/day up to 300 mg/day (MTD)**

System Organ Class	Adverse Reaction	Severity	Number of cases (F
Gastrointestinal disorders	Diarrhea	Mild to moderat	17 (2.8%)
	Vomiting	Mild to moderat	9 (1.5%)
General disorders and administration site conditions	Fatigue / Asthenia	Mild to moderat	17 (2.8%)
Investigations	Hepatic enzymes increased	Mild to severe	13 (2.1%)
	Blood creatine phosphokinase	Mild to moderat	6 (1.0%)
Musculoskeletal and connective tissue disorders	Myalgia	Mild to severe	9 (1.5%)
Metabolism and nutrition disorders	Decreased appetite	Mild to severe	9 (1.5%)
Nervous system disorders	Dizziness	Mild to moderat	6 (1.0%)
Skin and subcutaneous tissue disorders	Rash	Mild to moderat	8 (1.3%)
Renal and urinary disorders	Renal failure/impairment	Mild to moderat	7 (1.1%)

Among the non-serious adverse reactions, the most frequent were gastrointestinal disorders and general disorders. The first ones consisted mostly of diarrhea, and vomiting. For general disorders, the main symptoms were fatigue / asthenia. These are considered common and expected.

Other non-serious adverse reactions reported in more than 1% of patients concerned changes in biological parameters such as liver enzymes increase (mainly AT), CPK elevation, or increase of creatinine (reported by investigators as renal failure and/or impairment due to the calculation of creatinine clearance by MDRD based on creatinine). Myalgia, decrease of appetite dizziness and rash were also reported in more than 1% of patients but remain limited.

Regarding specific monitoring, although no signal for increase in CPK has been observed in the clinical trials, given the known effects of PPARα agonists on the increase of CPK enzyme, this parameter is monitored in clinical trials. For this reason, it is recommended that investigators review these lab results in the course of clinical trials.

Other known effects of PPARα agonists include the increase of creatinine, which was observed in our phase IIa and IIb trials, in a range of 5-10%. This increase was reversible at end of treatment. This should also be monitored in clinical trials.

Liver enzymes will also be monitored in clinical trials, with specific attention paid to DILI.

Based on the findings of nonclinical reproductive and developmental toxicity studies performed to date, and in the absence of human pregnancy data, elafibranor may be classed in the "Possible human teratogenicity/fetotoxicity in early pregnancy" risk category according to the Clinical Trial Facilitation Group (CTFG) document Recommendations related to contraception and pregnancy testing in clinical trials (September 2014)[34].

As such, all clinical trials with elafibranor including WOCBP request a negative pregnancy test before Randomization, with highly effective contraceptive measures throughout the study. It is recommended to maintain the contraception up to 1 month after end of treatment. Pregnancy tests should be repeated as stated in each study protocol.

6.6.2. Safety data conclusion

Based on the cumulative experience gathered to date, gastro-intestinal disorders and asthenia / fatigue are considered common non-serious adverse reactions reasonably associated with elafibranor. Most of them are of mild to moderate intensity. Laboratory increases in serum creatinine or CPK should be monitored throughout clinical trials as this has been observed in Phase II trials to date, and is a known PPARα agonist effect. Elevation of AT will be monitored as well as DILI. In the absence of extensive human pregnancy data, highly effective contraception should be maintained for women of childbearing potential participating in clinical trials with elafibranor treatment, up to 1 month after end of study treatment.

6.6.3. Benefit/risk assessment

Numerous Phase I and Phase IIa clinical studies have provided data that support the therapeutic potential of elafibranor in metabolic diseases including NASH. Moreover, the Phase IIb trial demonstrated the efficacy of elafibranor at the therapeutic dose of 120 mg on a clinically meaningful primary endpoint, resolution of histological NASH without worsening of fibrosis, in patients with active disease (NAS ≥4). While the trial was short and not designed for antifibrotic endpoints, it nonetheless showed that elafibranor, at 120 mg daily, improved fibrosis indirectly through the resolution of NASH. Importantly, elafibranor 120 mg concomitantly improved the cardiometabolic risk profile of the patients by decreasing plasma triglycerides, total and LDL-cholesterol, increasing HDL-cholesterol, and improving inflammation, insulin resistance, and glucose homeostasis. Together these results position elafibranor as a drug candidate to treat NASH with the objective to block fibrosis evolution and ultimately avoid long term liver outcomes while reducing cardiovascular risk.

Furthermore, the Phase IIa trial in PBC subjects who had an inadequate response to UDCA demonstrated similar improvement in GGT, lipid and inflammatory markers. Moreover, a significant decrease of ALP levels was observed, resulting in significant treatment effects versus placebo on the primary endpoint, whilst also meeting the composite endpoint used for drug registration (i.e. serum ALP <1.67 x ULN, an ALP decrease >15% and total bilirubin <ULN).

Moreover, these studies have highlighted the good safety profile of elafibranor and no major safety concerns have been raised.

Despite this favorable benefit-risk profile, an independent DSMB is to be established in order to review the safety of the treatment during the trial in an unblinded manner, to protect patient welfare and preserve study integrity. The safety assessments will be performed on a regular basis, every 6 months after Randomization of the first patient. The DSMB will consist of 5 experienced physicians (1 endocrinologist, 1 cardiologist, 1 hepatologist, 1 oncologist, and 1 nephrologist) and 1 statistician, all independent of the participants in the study.

In addition, throughout the study, patients will benefit from close safety monitoring including assessment of many safety parameters and follow-up of the disease progression, mainly through noninvasive measures including FibroScan.

7. TREATMENTS

7.1. DESCRIPTION OF STUDY MEDICATIONS

Elafibranor (propanoic acid, 2-[2,6-dimethyl-4-[3-[4-(methylthio)phenyl]-3-oxo-1(E)-propenyl] phenoxy]-2- methylpropanoic acid) will be supplied as 120 mg white to off-white round coated tablets with no printed inscription. The tablet contains elafibranor and inactive ingredients [redacted]

Placebo to match elafibranor 120 mg will be provided as a white to off-white round coated tablet with no printed inscription.

For additional information see Investigator's Brochure.

7.2. PACKAGING AND LABELING

7.2.1. Packaging

Elafibranor/placebo:

The primary packaging is composed of opaque polyamide/aluminum/PVC complex and aluminum foil blisters. This has been shown to be a suitable primary packaging for tablets.

Blisters, containing 8 tablets each, will be packed in child proof wallets.

Each childproof wallet will contain 4 blisters. Three wallets will be packaged inside a carton.

7.2.2. Labeling

All labels for study drugs meet all applicable requirements of the US Food and Drug Administration (FDA) and the EU annex 13 of Good Manufacturing Practices: Manufacture of Investigational Medicinal Products (February 2010) and /or other local regulations, as applicable.

Distribution of study drug will be performed according to the Good Distribution Practices.

Product cartons will be labeled with the protocol number, Sponsor's name and address, description of contents, storage conditions, expiry date, dosage instructions, and any other applicable items required by national and regional guidelines/regulations. The label will contain the statements "For clinical trial use only" or other similar/appropriate statements as well as the following instructions "Please return empty packaging and unused products to your doctor at your next visit." Details of carton and wallet labels are detailed in APPENDIX V: Product carton and wallet labeling.

7.3. DOSAGE AND ADMINISTRATION OF ELAFIBRANOR AND PLACEBO

Patients will be informed to take one tablet per day of elafibranor 120 mg or placebo orally before breakfast with a glass of water each morning.

7.4. METHOD OF ASSIGNING PATIENT TO TREATMENT GROUP

Upon screening of the first patient, the IXRS system will immediately forward the information to the Drug Distribution Center which will be responsible to send one of several blocks of treatment packages (containing 96 tablets to last approximately 3 months) allocated to the site. The pharmacy will acknowledge receipt of the study drug in the IXRS.

An e-mail, confirming that the patient has been screened, will be sent to the Investigator, [redacted] and to the Sponsor.

After having received the liver biopsy results as well as the SV1 laboratory results (SB1) (or when applicable, results of any retesting performed), and if the patient fulfills all criteria to enter the treatment period, the Investigator will register the patient in the IXRS to randomize him/her.

The IXRS will check if the Investigator is authorized to use the system (identification number and access code) and will ask some questions to check the patient eligibility. The IXRS will then allocate the patient to a treatment group (elafibranor 120 mg or placebo) through a patient number (with 9 digits), as described in Section 3.2.

A specific IXRS procedure manual will be provided to the pharmacy.

The randomization list will be generated by the IXRS partner and will be kept in blinding condition to the study participants until the final database lock and the Sponsor authorization to unblind the trial.

7.5. STORAGE CONDITIONS

Elafibranor and placebo should be stored between +15°C and +25°C (59°F and 77°F). Storage conditions are specified on the label.

7.6. DISPENSING OF TREATMENT

Each site will have a resupply strategy within the IXRS to determine the supply of study drugs sent to each site. Initial site shipments will be shipped at a static value defined in the supply strategy. Following randomization of a patient IXRS will project for the amount of study drug required for future visits and ensure the study drug is at site for the visits occurring. The IXRS will continue to project study drug requirements per patient until an event occurs which stops the projections for that patient.

The Investigator will register the patient's visit in the IXRS who will allocate to the patient a treatment

package for approximately 3 months (96 tablets) in the First Treatment Period and for approximately 6 months (192 tablets) in the LTTP. An e-mail, confirming the registration, will be sent to the Investigator and to the Sponsor.

The treatment package will include a carton with 3 wallets of 4 blisters for the First Treatment Period and 2 cartons with 3 wallets of 4 blisters in the LTTP.

Each randomized patient will be given, from V1 and at every following visit, the study medication containing the adequate number of wallets to cover the drug administration for the period between visits. The time between visits will be 12 weeks ± 1 week (to a maximum of 96 days) during the First Treatment Period and 24 weeks ± 2 weeks (to a maximum of 192 days) between visits in the LTTP, which correspond to the number of tablets provided to the patient at each visit.

7.7. TREATMENT REPLACEMENT

A specific IXRS procedure manual will be provided to the Investigator and will detail the procedure in case of need of treatment replacement.

7.8. PROCEDURE FOR BLINDING

The Investigator, patient, and study personnel will be blinded to the treatment.

Identification numbers will be assigned to a patient at the Screening Visit. The number will also be reported in the eCRF. Upon completion of the Screening Visit(s), eligible patients will be randomly assigned to active treatment (elafibranor 120 mg) or placebo at the first visit of the First Treatment Period (V1).

7.9. PROCEDURE FOR UNBLINDING

The randomization code may be broken by the Investigator when urgent action is required for the clinical management of the patient. For each patient, the list of treatment numbers allocated to the patient will be stored in the IXRS. The Investigator will be able to unblind any treatment carton that was dispensed to the patient by connecting to the IXRS (**24-hour & 7-day access**) and entering their identification number and access code. A back-up phone Interactive Response Technology (IRT) module will also be available should the site be unable to access the internet. The IXRS will verify the authorization to unblind the entered treatment carton and the screen will then display the treatment group, when completed, a blinded confirmatory e-mail will be sent to the Investigator and the Sponsor.

The reason for unblinding should be clearly and fully documented by the Investigator.

7.10. STUDY DRUG COMPLIANCE

From V2 and at every following visit while the patient is being treated with study drug, the patient will be directed to bring back all used and unused cartons and blisters. Compliance will be checked by the Investigator during those visits and registered in the eCRF.

If treatment is interrupted, whatever the cause, duration and reason of the interruption should be documented.

7.11. TREATMENT ACCOUNTABILITY, RETRIEVAL AND DESTRUCTION

The Investigator or pharmacist will acknowledge receipt for each study treatment on the day of receipt. A drug accountability record should be maintained by the person responsible for dispensing the trial medication to the patient.

All partially used or unused treatments will be inventoried by the monitor during and at the conclusion of the study.

On Sponsor request, the Drug Distribution Center will organize the retrieval of all treatments (used or unused) and will proceed to their destruction only after the Sponsor provides written authorization.

If the site has an appropriate Standard Operating Procedure (SOP) for drug destruction, the site may destroy used and unused study drugs in accordance with the site SOP and always after the drug accountability has been performed by the monitor.

If drug is destroyed in the site, the Investigator must maintain accurate records for treatment cartons destroyed recording:

- Treatment carton (kit) number (see APPENDIX V: Product carton and wallet labeling)
- Quantity destroyed
- Method of destruction
- Person who disposed the drug.

7.12. OTHER MEDICATION

7.12.1. Handling of concomitant medication

In a general manner, patients should be discouraged from starting any new medication without consulting the Investigator unless the new medication is required for emergency purpose. In the same way, any qualitative or quantitative change in concomitant therapy should be avoided, when possible (see table II, APPENDIX III: Permitted/non-permitted medication). In the event that it becomes necessary during the study, this should be recorded by the Investigator in the eCRF (including concomitant medications taken within 6 months prior to Screening) and information should be communicated to the Medical Monitor in order to evaluate the risk of DDIs. This includes drugs used on a chronic as well as on an "as needed" basis.

7.12.2. Non-permitted medication

The following medications are not allowed within the timeframe given in APPENDIX III: Permitted/non-permitted medication):

- Thiazoledinediones (glitazones [pioglitazone & rosiglitazone])
- Fibrates
- Corticosteroids (parenteral & oral chronic administration only)
- Amiodarone
- Tamoxifen
- Methotrexate
- Indomethacin.

The following medications are not allowed to be initiated prior to diagnostic liver biopsy and up to 72 weeks of treatment (see APPENDIX III: Permitted/non-permitted medication):

- GLP-1 agonist
- SGLT2 inhibitors.

If it is identified that these non-permitted drugs have been administered to a patient within the excluded timeframes, the site will discuss the continuation of the patient with the Medical Monitors of the study.

7.12.3. Permitted medication under condition

The following medications are permitted under the condition of steady dosage prior to Screening (dose changes are allowed after Randomization if judged necessary by the physician (see APPENDIX III: Permitted/non-permitted medication)):

- Statins, ezetimibe, and other nonfibrate lipid lowering medications, provided the dosage is kept stable for at least 2 months prior to Screening.

The following medications are permitted under the condition of stable dose from at least 6 months prior to diagnostic liver biopsy (dose changes should be avoided up to EOT):

- Vitamin E >400 IU/day
- PUFAs >2 g/day
- UDCA.

The following medications are permitted under the condition of no qualitative change (i.e., implementation of a new antidiabetic drug) in the 6 months prior to diagnostic liver biopsy and up to Randomization:

- Insulin
- Sulfonylureas
- Metformin
- Gliptins
- SGLT2-inhibitors
- GLP-1 agonists.

Dose changes are allowed for these medications, except for GLP-1 agonists, which must be on stable dose in the 6 months prior to diagnostic liver biopsy and up to randomization.

In addition, no initiation of SGLT2-inhibitors and GLP-1 agonists is allowed from at least 6 months prior to the diagnostic liver biopsy up to 72 week of treatment (V7).

Patients on sulfonylureas and insulin are recommended to self-monitor blood glucose.

7.12.4. Permitted medication

Any medications other than those listed above are permitted. However, the dosage of a current medication for a chronic disease should remain unchanged as far as possible in order to reduce the risk of unknown DDIs.

In the event that additional concomitant therapy becomes necessary during the study, this should be recorded by the Investigator in the eCRF. This includes drugs used on a chronic as well as on an "as-needed" basis. Patients should be discouraged from starting any new medication without consulting the Investigator unless the new medication is required for emergency purpose.

8. ADVERSE EVENT AND TOXICITY MANAGEMENT

8.1. DEFINITIONS

8.1.1. Adverse events

Any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical (investigational) product and which does not necessarily have to have a causal relationship with this treatment will be considered as an AE. The term AE is synonymous with the term "adverse experience" as used by the FDA.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding or physiological observation, for example), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal product.

Examples of AE include (but are not limited to): abnormal test findings; clinically significant symptoms and signs; changes in physical examination findings; hypersensitivity; progression/worsening of pre-existing condition or underlying disease; recurrence of a pre-existing condition; lack of effect, complication, and termination of pregnancy.

Additionally, they may include the signs or symptoms resulting from: drug overdose, drug withdrawal, drug abuse, drug misuse, drug interactions, drug dependency, extravasation, exposure in utero.

The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

- Test result is associated with accompanying symptoms
- Test result requires additional diagnostic testing or medical/surgical intervention
- Test result leads to a change in trial dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy
- Test result is considered to be an AE by the Investigator or Sponsor.

Repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

An AE does not include the following:

- Medical or surgical procedures performed; the condition that leads to the procedure may be an AE if applicable
- Pre-existing disease, condition or laboratory abnormalities present or detected before the Screening Visit that do not worsen
- Overdose without clinical sequelae
- Any medical condition, or clinically significant laboratory abnormality with an onset before the

consent form is signed. Such as medical condition is considered to be pre-existing and should be documented on the medical history of the eCRF

- Uncomplicated pregnancy
- An induced elective abortion to terminate a pregnancy without medical reason
- Events that are identified as efficacy endpoints for the long-term evaluation (described in Section 1.9.2) should not be reported as AE.

The questions concerning whether the condition existed before the start of the active phase of the study and whether it has increased in severity and/or frequency will be used to determine whether an event is a treatment-emergent AE. An AE is considered to be treatment emergent if (1) it is not present when the active phase of the study begins and is not a chronic condition that is part of the patient's medical history, or (2) it is present at the start of the active phase of the study or as part of the patient's medical history, but the severity or frequency increases during the active phase. The active phase of the study begins at the time of the first dose of the study drug. The active phase of the study ends at the last study visit.

8.1.2. Adverse events of special interest (AESIs)

AESIs are treatment emergent AEs corresponding to the conceptual definition of:

- CPK elevations of severe intensity or leading to permanent study drug discontinuation
- Muscle injury symptoms of severe intensity corresponding to:
  - Muscle pain or Myalgia
  - Muscle spasms or Tremor
  - Muscle weakness
- Transaminases elevations from baseline of severe intensity or leading to permanent study drug discontinuation
- Liver injury events of severe intensity corresponding to:
  - Hepatic impairment
  - Hepatic failure
- Gastrointestinal symptoms of severe intensity corresponding to:
  - Abdominal pain
  - Constipation
  - Diarrhea
  - Nausea
  - Vomiting
  - Acute cholecystis
  - Acute pancreatitis
- Fatigue and Asthenia of severe intensity
- Serum creatinine elevations of severe intensity or leading to permanent study drug discontinuation
- Renal injury events of moderate or severe intensity corresponding to:

- Renal failure
- Renal impairment
- Renal colic

Treatment emergent Pregnancy and outcomes of Pregnancy will be considered as AESIs, and are described in the section 8.6.1.

8.1.3. Serious adverse events

A SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (see Section 8.1.3.1)
- Requires inpatient hospitalization or prolongation of existing hospitalization (see Section 8.1.3.2)
- Results in persistent or significant disability/incapacity (see Section 8.1.3.3)
- Is a congenital anomaly/birth defect (including fetal malformations associated with spontaneous abortions or elective abortions)
- Is another medically important condition (see 8.1.3.1 8.1.3.4).

In addition, any illnesses reported before starting active treatment or AE meeting the criteria of seriousness (as defined above) and considered to be possibly related (according to the Investigator) to any study-specific procedure (e.g., laboratory testing procedure, liver biopsy) must be reported as an SAE.

8.1.3.1 Life-threatening adverse events

- A life-threatening AE in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

8.1.3.2 Inpatient or prolonged hospitalization

An inpatient hospitalization or prolongation of a hospitalization means that the patient stays overnight in the hospital. An overnight stay is defined by hospitalization of 24 hours. Visits to the emergency room will not be considered hospital admission. Pre-planned hospital stays or hospital stays for nonmedical social reasons will not be considered as hospitalization, for example:

- Hospitalization or prolongation of hospitalization is needed for a procedure required by the protocol. Day or night survey visits for biopsy or surgery required by the protocol are not considered serious.
- Hospitalization or prolongation of hospitalization is part of a routine procedure followed by the study center (e.g., stent removal after surgery). This should be recorded in the study file.
- Hospitalization for survey visits or annual physicals fall in the same category.

- Hospitalization planned before the start of the study for a pre-existing condition that has not worsened does not constitute an SAE (e.g., elective hospitalization for a total knee replacement due to a pre-existing condition of osteoarthritis of the knee that has not worsened during the study).

8.1.3.3 Significant or incapacitating disability

Only a persistent or significant or incapacitating disability is intended. This item refers to a substantial disruption of a person's ability to conduct normal life functions. Thus, disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma.

8.1.3.4 Medically important conditions

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

Examples of such events are:

- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias or convulsions that do not result in hospitalization
- Development of drug dependency or drug abuse.

8.1.4. Clarification on serious adverse events:

- Events that are identified as primary efficacy endpoints for the long-term evaluation should not be included as an AE.
- Death is an outcome of an AE, not an AE in itself.
- An SAE may occur even if the patient was not being treated with the investigational medicinal product at the occurrence of the event.
- Life-threatening means that patient is at immediate risk of death. This does not include an event that might have led to death if it had occurred with greater severity.
- Complications that occur during hospitalizations are AEs. If a complication prolongs the hospitalization, it is a SAE.
- Patient hospitalization means that the patient stays overnight in the hospital. Pre-planned hospital stays or hospital stays for nonmedical social reasons will not be considered as hospitalization.
- A procedure for protocol/disease-related investigations (e.g., biopsy) should not be reported as SAE. Hospitalization or prolonged hospitalization for a complication of such procedures should be reported as SAE.

8.1.5. Adverse drug reaction

An adverse drug reaction (ADR) is defined as a response to a medicinal product which is noxious and unintended and that is considered casually related to an investigational medicinal product. A serious ADR (SADR) is an ADR which meets the seriousness criteria.

8.1.6. Unexpected adverse event

Expectedness is assessed by the Sponsor. An unexpected AE is defined as an event that has a nature of severity or specificity that is not consistent with the applicable Investigator Brochure or that is symptomatically and pathophysiologically related to a known toxicity but differs because of a greater severity or specificity.

"Unexpected" refers to an ADR that has not been previously observed and reported rather than an event that has not been anticipated based on the properties of the drug.

8.2. ASSESSMENTS

The Investigator will establish whether or not any AE have occurred at each visit from the date of consent. The patient will be questioned in a general manner to determine specific symptoms without offering the patient any suggestion.

8.2.1. Intensity assessment

The intensity of the AE will be graded as follows:

- **Mild**: Awareness of signs or symptoms, but easily tolerated and are of minor irritant type causing no loss of time from normal activities. Symptoms do not require therapy or a medical evaluation; signs and symptoms are transient.
- **Moderate**: Events introduce a low level of inconvenience or concern to the participant and may interfere with daily activities, but are usually improved by simple therapeutic measures; moderate experiences may cause some interference with functioning.
- **Severe**: Events interrupt the participant's normal daily activities and generally require systemic drug therapy or other treatment; they are usually incapacitating.

8.2.2. Relation to the study treatment

The Investigator will make a clinical and scientific judgment regarding whether or not the AE was related to study treatment. The Investigator will evaluate any changes in laboratory values, make a determination as to whether or not the change is clinically important, and whether or not the changes were related to study drug. However, even if the Investigator feels there is no relationship to the study drug, the AE or clinically significant laboratory abnormality must be recorded in the eCRF.

The Investigator will record the relation to the study treatment according to the following causality terms:

- **Related:** the AE follows a reasonable temporal sequence from the time of drug administration and it cannot be explained by the patient's clinical state or the study procedures/conditions. The AE abates upon discontinuation of the study drug and reappears when the study drug is introduced.
- **Possibly related:** the AE follows a reasonable temporal sequence from the time of drug administration, but could have been produced by the patient's clinical state or the study procedures/conditions.
- **Unlikely related:** the temporal association between the AE and the study drug is such that the study drug is not likely to have any reasonable association with the AE. The relationship is not likely because of other plausible explanations.
- **Not related:** the AE must definitely be caused by the patient's clinical state or the study procedure/conditions. A reasonable explanation must be given, e.g., no investigational product taken, preplanned elective medical intervention, or incompatible temporal relationship.
- **Not assessable**: the report suggesting an adverse reaction cannot be judged because information is insufficient or contradictory and data cannot be supplemented or verified.

8.2.3. Action taken and outcome

The Investigator will record the action taken with drug and outcome of the event for each AE according to the following:

Action taken with investigational drug

- Drug permanently withdrawn – in case a patient is permanently withdrawn from the study drug
- Drug temporarily withdrawn – in case the study drug is temporarily withdrawn
- Dose not changed – in case no action is taken regarding the study drug
- Unknown
- Not applicable – an AE started before initiation of treatment with study drug, the treatment had been completed prior to reaction/event, or the patient has died.

Outcome

- Recovered/resolved
- Recovering/resolving
- Not recovered/not resolved
- Recovered/resolved with sequelae
- Fatal
- Unknown.

Note: In case of irreversible congenital anomalies the choice not recovered/not resolved should be used. "Fatal" should be used when death is possibly related to the reaction/event.

8.3. REPORTING

8.3.1. Reporting an adverse event

All AEs regardless of seriousness or relationship to study drug, including those occurring during the Screening Period, are to be recorded on the corresponding page(s) of the eCRF and in the patient's medical record from the ICF signature until study end for each patient. Whenever possible, symptoms should be grouped as a single syndrome or diagnosis. The Investigator should specify the date of onset, maximal intensity, action taken with respect to study drug, corrective therapy given, outcome, and his/her opinion as to whether there is a reasonable possibility that the AE was caused by the study drug.

Adverse event reporting begins from signature of the patient ICF at the first Screening Visit and ends at study end for each patient.

8.3.2. Reporting a serious adverse event or an adverse event of special interest

Serious AE reporting begins from signature of the patient ICF and ends at study end for each patient.
AESI reporting starts from first study drug intake and ends at study end for each patient.

Any SAE or AESI that is brought to the attention of the Investigator at any time after the reporting period and which is considered by him/her to be caused by the study drug within a reasonable possibility, should be reported.

Any of the portal hypertension/cirrhosis related events described in Section 2.1.2 that are identified as potential primary efficacy endpoints for long-term evaluation will NOT be reported as SAEs unless it is determined by the adjudication committee that the event does not meet the predefined criteria for an endpoint. Events that are identified as potential primary efficacy endpoints for long-term evaluation that are not confirmed by adjudication will be reported as described with the start of the reporting time window being the time of negative adjudication decision.

Investigators must notify, by e-mail or fax, the Sponsor designated representative [redacted] (LSS) Medical Affairs of all SAEs or AESIs **IMMEDIATELY (within 24 hours of the Investigator becoming aware of the event).**

ANY SERIOUS ADVERSE EVENTS, OR ADVERSE EVENTS OF SPECIAL INTEREST, WHETHER OR NOT RELATED TO THE STUDY DRUG, MUST BE REPORTED IMMEDIATELY (WITHIN 24 HOURS) TO [redacted] AT THE FOLLOWING FAX NUMBERS:

FAX numbers: [redacted]

Contact Person: [redacted]

E-mail: [redacted]

All SAEs or AESIs independent of the circumstances or suspected cause must be reported in ENGLISH on a SAE Form. The SAE/AESI Form should include a clearly written narrative describing signs, symptoms, intensity and treatment of the event, diagnostic procedures, as well as any relevant laboratory data and any sequelae, in order to allow a complete medical assessment of the case and independent determination of the possible causality.

The Investigator is also required to submit follow-up SAE/AESI reports to [redacted] within 24 hours of becoming aware of additional information such as diagnosis, outcome, causality assessment, results of specific investigations, and any new significant information that has not been previously reported.

It is critical that the information provided on the initial or follow-up SAE/AESI Form matches the information recorded in the source documents and the eCRF for the same event.

Copies of additional laboratory tests, consultation reports, postmortem reports, hospital case reports, autopsy reports, and other documents should be sent when requested and applicable. All provided reports must be anonymized.

Follow-up reports relative to the patient's subsequent course must be submitted to [redacted] until the event has subsided or, in case of permanent impairment, until the condition stabilizes.

The Sponsor or its designated representative will report all the relevant safety information to the concerned Competent Authorities and to the Independent Ethics Committee(s) (IRB/IEC) according to the country-specific requirements.

Investigator must fulfill his/her regulatory obligations to the Regulatory Authorities and/or to the Ethics Committee in accordance with local regulations.

Depending on local regulations in different regions and countries, the Sponsor or designated clinical research organization (CRO) may be required to expedite report to the Regulatory Authorities for:

- SAEs (including events related to study procedures)
- SADRs (a serious ADR)
- SUSARs (Suspected unexpected serious adverse reactions)

Each SAE report received from the Investigators will be evaluated by the designated CRO for pharmacovigilance who will assess the seriousness of the event. Each SAE report will be evaluated by the Sponsor and/or his designees who will assess the relationship to study procedure or study treatment and the expectedness of the event. Expectedness will be assessed using the reference safety information included in the Investigator Brochure.

Any unexpected safety issue that changes the risk benefit analysis and is likely to have an impact on the patients who have participated in the trial will be reported by the Sponsor as soon as possible to the

Competent Authority(ies) concerned together with proposed actions.

8.3.3. Follow-up

The Investigator should take all appropriate measures to ensure the safety of the patients, notably he/she should follow up the outcome of any AE until the return to normal or until stabilization of the patient's condition.

The patient must be followed up until clinical recovery is complete and laboratory results have returned to normal, or until progression has been stabilized. This may imply that follow-up will continue after the patient has left the study (i.e. after EoT visit), notably for the potential related adverse events, and that additional investigations may be requested by the Sponsor. This information should be documented in the patient's medical records.

8.4. POST STUDY REPORTING REQUIREMENTS

Any SAEs and deaths that occur within 30 days of the last dose of the study drug, regardless of causality, should be reported.

Any SAE that is brought to the attention of the Investigator at any time after the reporting period and which is considered by him/her to be caused by the study drug within a reasonable possibility, should be reported.

8.5. CLINICAL LABORATORY ABNORMALITIES AND OTHER ABNORMAL ASSESSMENTS AS ADVERSE EVENTS OR SERIOUS ADVERSE EVENTS

Laboratory abnormalities are not necessarily recorded as AEs or SAEs. However, laboratory abnormalities that are considered clinically relevant by the Investigator must be recorded as an AE, AESI or SAE as applicable.

8.6. SPECIAL SITUATION REPORTS

Special situations reports include pregnancy reports, reports of medication error, abuse, misuse or overdose, and reports associated with product complaints.

8.6.1. Pregnancy

In case of pregnancy a communication will be sent by the Investigator to [redacted] by faxing a completed pregnancy form within 24 hours of his/her knowledge of the pregnancy.

Pregnancies of females partners of male patients exposed to study medication should also be reported to [redacted] using the corresponding pregnancy form, provided that pregnant female partners have signed an informed consent.

Female patients must be instructed to discontinue the study drug immediately and inform the Investigator as soon as possible once they are aware of being pregnant or suspect that they are pregnant during the study or within 30 days of the last dose of the study drug.

Female patients will be requested, as part of the general ICF, to provide informed consent to allow reasonable attempts to be made to obtain information on any possible medicinal product exposure to an embryo or fetus and to follow up on the outcome of the pregnancy.

The Investigator will contact the patient at the expected time of delivery for follow-up. If the outcome of pregnancy meets the criteria for immediate classification of an SAE (e.g., spontaneous or therapeutic abortion, stillbirth, neonatal death, congenital anomaly, birth defect), the Investigator should follow the procedure for reporting SAEs as detailed in Section 8.3.2.

8.6.2. Medication error

Medication error is defined as an unintentional error in the prescribing, dispensing, or administration of a medicinal product while in the control of the healthcare professional, patient, or consumer. All medication errors will be documented in the eCRF and, in case of any potential risk to patient safety, would be reported as appropriate (see Section 8.3).

8.6.3. Misuse

This refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the authorized product information and will be reported in the eCRF. All misuse will be documented in the eCRF and, in case of any potential risk to patient safety, would be reported as appropriate (see Section 8.3).

8.6.4. Overdose

This refers to the administration of a quantity of a medicinal product given per administration or cumulatively, which is above the maximum recommended dose according to the authorized product information (see Section 8.1.1 and Section 8.3.1). Clinical judgment should always be applied.

8.6.5. Abuse

This corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

9. STATISTICAL METHODS AND DATA ANALYSIS

This section is an overview of the key elements of the statistical analysis for this study. Further details on statistical reporting and analyses will be contained in a separate statistical analysis plan (SAP). This SAP may be revised during the study only to accommodate protocol amendments and to make changes to adapt to unexpected issues in study execution and data collection that could affect planned analyses. In all circumstances, a final SAP should be issued prior to database lock and treatment unblinding. The first approved version of the SAP should be available within 3 months of first patient randomized and before the first DSMB meeting.

The main analyses will be based on patients with fibrosis stage F2 and F3. The summaries will be repeated in an exploratory manner with the inclusion of patients with fibrosis stage F1.

9.1. RANDOMIZATION AND TREATMENT ASSIGNMENT

Random allocation will be made to the 2 treatment groups (elafibranor and placebo) in a 2:1 ratio basis and stratified by the following factors:

- Type 2 diabetes (yes, no)
- Gender (male, female) (with a capping of women to 40%)
- Fibrosis stage (F1, F2, F3) (capped to 202 F1 patients).

Details on the randomization process are in Section 3.2.

9.2. ENDPOINTS

9.2.1. Surrogate endpoint - resolution of NASH

The first surrogate endpoint for this study is resolution of NASH without worsening of fibrosis after 72 weeks of treatment. Resolution of NASH is defined as the disappearance of ballooning (i.e., grade 0) and disappearance or persistence of minimal lobular inflammation (i.e., grade 0 or 1) with an overall pattern of injury not qualifying for steatohepatitis. Worsening of fibrosis is evaluated using NASH CRN fibrosis staging system and defined as progression of at least 1 stage. This surrogate endpoint will be formally assessed at the time of the surrogate efficacy analysis when at least the first 1023 randomized F2 and F3 patients complete the 72 week treatment period or discontinue early from the study treatment (see Section 9.8.1 for details). An additional exploratory analysis of this endpoint will take place at the time of the final analysis.

9.2.2. Long-term endpoint – time to clinical event/death

The long term endpoint of clinical outcomes is a composite endpoint composed of death due to any cause, histological liver cirrhosis, and the full list of portal hypertension/cirrhosis related events:

- Liver transplantation
- MELD score ≥15 for patients with baseline MELD score ≤12

- the onset of:
  - variceal bleed requiring hospitalization,
  - hepatic encephalopathy defined as West Haven/Conn score ≥2 and requiring hospitalization,
  - spontaneous bacterial peritonitis,
  - ascites requiring treatment.

The final analysis will be performed when 456 patients experience an event listed above. This is expected to occur approximately 96 months after the first patient is randomized.

9.2.3. Key Secondary Endpoints

The key secondary endpoints are:

- Percentage of patients with improvement of fibrosis of at least 1 stage according to NASH CRN scoring at 72 weeks.

To assess the clinical benefit after 72 weeks of treatment on the following metabolic endpoints:

- Changes from baseline to Week 72 in triglycerides, Non-HDL cholesterol, HDL cholesterol, LDL cholesterol, HbA1c (in diabetic patients), HOMA-IR (in non-diabetic patients)

These key secondary endpoints will be assessed at the time of the surrogate endpoint analysis (at least the first 1023 randomized patients with fibrosis stage F2 and F3) for the resolution of NASH without worsening of fibrosis endpoint.

9.2.4. Other Secondary Endpoints

The other secondary endpoints are:

- To assess histological changes after 72 weeks of treatment and at the end of the LTTP on the following endpoints:
  - percentage of patients with resolution of NASH without worsening of fibrosis (at the end of LTTP)
  - percentage of patients with improvement of fibrosis of at least 1 stage according to NASH CRN scoring (at the end of LTTP)
  - percentage of patients with improvement of fibrosis of at least 1 stage according to NASH CRN scoring without worsening of NASH
  - percentage of patients with no worsening of Fibrosis and no worsening of NASH
  - percentage of patients with resolution of NASH and improvement of Fibrosis
  - percentage of patients with at least a 1 point improvement in histological scores (NASH CRN scoring: NAS [sum of steatosis, hepatic ballooning and lobular inflammation], steatosis, hepatic ballooning, lobular inflammation), fibrosis (NAFLD Ishak scoring system), or portal inflammation

- percentage of patients with improvement of NAS of at least 2 points
- percentage of patients with improvement of NAS of at least 2 points and with at least 1 point improvement in hepatic ballooning
- percentage of patients with at least a 1 point improvement in disease activity score (sum of ballooning and lobular inflammation scores) according to NAS scoring and steatosis-activity- fibrosis (SAF) scoring
- percentage of patients with at least a 1 point improvement in disease activity score (sum of ballooning and lobular inflammation scores) according to NAS scoring and with at least 1 point improvement in hepatic ballooning
- percentage of patients with at least a 1 point improvement in disease activity score (sum of ballooning and lobular inflammation scores) according to steatosis-activity-fibrosis (SAF) scoring and with at least 1 point improvement in hepatic ballooning
- percentage of patients with at least 2 points improvement in disease activity score according to NAS scoring and SAF scoring
- changes in NAS, fibrosis (using NASH CRN and NAFLD Ishak scoring system), steatosis, hepatic ballooning, lobular inflammation, portal inflammation and SAF activity score
- changes in area of fibrosis (normalized Collagen Proportional area in %) by morphometry.

- To assess the following endpoints at Week 72 and at the end of the LTTP:
  - changes in liver enzymes and liver markers
  - changes in noninvasive markers of fibrosis and steatosis
  - changes in lipid parameters
  - variation in body weight
  - changes in insulin resistance and glucose homeostasis markers
  - changes in inflammatory markers
  - changes in cardiovascular risk profile as assessed by Framingham scores
  - changes in liver stiffness by Fibroscan measurement
  - changes in quality of life (SF-36 questionnaire).
- To assess the onset to:
  - histological liver cirrhosis
  - death of any cause
  - any portal hypertension or cirrhosis related events
  - cardiovascular events
  - liver-related death events.

9.2.5. Exploratory endpoints

The exploratory endpoint is:

- To constitute a biobank for discovery and validation of biomarkers in

NASH. Details on all endpoints will be given in the SAP.

9.3. ANALYSIS SETS

The following analysis sets will be used in this study:

- Enrolled: all patients who sign informed consent. This set will be used to summarize disposition.
- ITT: all randomized F2 and F3 patients. This set will be used to summarize efficacy. The main analysis of the primary and key secondary endpoints will be based on the ITT.
- Safety set (SS): all F2 and F3 patients who receive at least 1 dose of study drug. This set will be used to summarize safety.
- Efficacy evaluable set (EES): All F2 and F3 patients in the ITT population who have taken at least one dose of study treatment and have a reliable liver biopsy at both baseline and at the end of the 72 week treatment period.
- Per protocol set (PPS): all F2 and F3 patients who receive at least 1 dose of study drug and do not have any important protocol deviations leading to exclusion from the PPS. Important protocol deviations will be defined in the SAP and agreed prior to database lock. Supportive analysis of the primary and key secondary endpoints will be based on the PPS.
- Exploratory F1 cohort: All randomized F1 patients who have taken at least 1 dose of study drug.
- Full Intent-To-Treat Set (FITT): all randomized patients.
- Full Safety Set (FSS): all r patients who receive at least 1 dose of study drug.

Patients in the ITT, FITT, EES, PPS, and exploratory F1 cohorts (study population and efficacy data) will be analyzed based on randomized treatment. Patients in the SS, FSS, and exploratory F1 cohorts (safety data) will be analyzed based on actual treatment received.

9.4. ANALYSIS OF PRIMARY ENDPOINTS

9.4.1. Resolution of NASH

The null hypothesis for resolution of NASH without worsening of fibrosis is that there is no difference in response rates between the elafibranor and placebo groups. The alternative hypothesis is that there is a difference in response rates between the elafibranor and placebo groups. The null hypothesis will be tested at the two-sided 0.01 alpha level.

The number and percentage of patients with resolution of NASH without worsening of fibrosis at the end of the 72 week treatment period will be summarized by treatment group. The main analysis will be performed using a logistic regression model, with fixed terms for treatment, type 2 diabetes (yes, no), gender (male, female), fibrosis stage (F2, F3) and baseline NAS. According to the method described in Ge et al. (2011)[36], the statistical model will be used to estimate the difference (elafibranor/placebo) in rate of resolution of NASH without worsening of fibrosis and its 99% CI. The main confirmatory analysis will be performed when at least the first 1023 randomized F2/F3 patients have completed the 72 week treatment period or discontinued early from the study treatment. The main analysis will be based on the ITT. Supportive analysis will be based on the EES and PPS.

Patients with missing data for resolution of NASH without worsening of fibrosis will be treated as a nonresponder for the main analysis. Supplementary analyses using multiple imputations and a pattern mixture model will be performed, as well as sensitivity analysis using a Cochran-Mantel-Haenszel test. Further details will be provided in the SAP.

9.4.2. Long-term endpoints

The null hypothesis is that there is no difference in the hazard ratio between the elafibranor and placebo treatment groups. The alternative hypothesis is that there is a difference in the hazard ratio between the elafibranor and placebo treatment groups. The null hypothesis will be tested at the two-sided 0.04 alpha level.

The data will be analyzed using a Cox proportional hazards model with fixed terms for treatment, type 2 diabetes, gender, fibrosis stage, and baseline NAS. The Cox proportional hazards model will be used to calculate the hazard ratio (elafibranor/placebo) and 96% confidence interval. This will be performed when at least 456 patients experience a clinical event/death. The time to clinical event/death will also be analyzed using an unadjusted Cox-proportional hazard's model, log rank test and a nonparametric randomization based analysis of covariance method proposed by Saville and Koch.[37]

The time to clinical event/death will be presented graphically using a Kaplan-Meier curve. The median time to first clinical event/death and 95% confidence interval will also be presented for each treatment group.

Missing data will be censored at the last known date.

The main analysis will be based on the ITT. Supportive analysis will be based on the PPS.

9.5. OTHER STATISTICAL ANALYSIS

9.5.1. Key secondary endpoint

The number and percentage of patients with improvement of fibrosis according to NASH CRN scoring at the end of the 72 week treatment period will be summarized separately by treatment group. The data will be analyzed using a logistic regression model, with fixed terms for treatment, type 2 diabetes, gender, fibrosis stage and baseline NAS by NASH CRN scoring. The analysis will be performed at the time of the surrogate endpoint analysis when at least the first 1023 randomized patients with fibrosis stage F2 and F3 have completed the 72 week treatment period or discontinued early from the study treatment. The null hypothesis will be tested at the two-sided 0.01 alpha level.

The key secondary efficacy endpoints will be tested only if the primary surrogate endpoint is statistically significant. A gatekeeping procedure will be constructed to control the overall Type I error rate for testing the key secondary efficacy endpoints at an overall two-sided alpha level of 0.01.

The main analysis will be based on the IIT. Supportive analyses will be based on the EES and PPS.

9.5.2. Other secondary endpoints

All other secondary endpoints will be summarized by treatment group using descriptive statistics. The main analysis will be based on the ITT.

Categorical endpoints will be analyzed using a logistic regression model in the same manner as resolution of NASH without worsening of fibrosis.

Time to event endpoints such as time to first cardiovascular event/death will be analyzed using the Cox proportional hazard's model in the same manner as time to clinical event/death.

Continuous endpoints will be analyzed using a repeated measures Analysis of Covariance (ANCOVA) model with fixed terms for treatment, type 2 diabetes, gender, fibrosis stage, baseline NAS, and time-point and treatment by time-point interaction. A compound symmetry covariance matrix will be used for this analysis. The statistical model will be used to calculate the mean treatment difference and 95% confidence interval. If the data does not meet the required assumptions for parametric tests, the data will be analyzed using a nonparametric analysis of covariance method of Zink and Koch.[41]

Further details will be in the SAP.

9.5.3. Subgroup analyses

Exploratory analyses of the primary and key secondary endpoints will be done for selected subgroups, including, but not limited to, the following:

- Presence of type 2 diabetes (yes, no)
- Gender (male, female)
- Fibrosis (F2, F3)
- Geographic region (North America, Europe, South America, Rest of World)
- Race (Caucasian, Other)
- Ethnicity (Hispanic, not Hispanic)
- Age (<60, ≥60 years).
- PNPLA3 (absence or presence of risk allele G [i.e. CC vs GG/CG], and within the at risk group, homozygous vs. heterozygous for the risk allel G [i.e. CG vs GG])
- Patients under statins (yes/no), defined as patients who have duration of IP exposure greater or equal to 60 days, with extent of exposure to statin greater than or equal to 30 days before the visit 7 biopsy date.

Forest plots will be generated for each of these endpoints for patients in the ITT population.

9.5.4. Exploratory analyses

Additional exploratory analyses of the efficacy data will be performed on the exploratory F1 cohort and

the FITT.

9.6. STRATEGIES TO CONTROL TYPE I ERROR

The overall type I error for the primary endpoints in this study is two-sided α=0.05. The alpha for the primary endpoints will be split 20%/80%, with two-sided α=0.01 for resolution of NASH and two-sided α=0.04 for time to clinical event/death.

The key secondary efficacy endpoints will be tested only if the primary surrogate endpoint is statistically significant at a two-sided 1% significance level. A gatekeeping procedure will be constructed to control the overall Type I error rate for testing the key secondary efficacy endpoints at an overall two-sided alpha level of 0.01.

The gatekeeping procedure will be detailed in the SAP and set up using the general method for building multi-stage parallel gatekeeping procedures in multiplicity problems with several families of null hypotheses (Dmitrienko and Tamhane, 2011, 2013).[38,39]

Statistical testing for all other secondary endpoints will be of exploratory nature.

As this is a single pivotal study that will be used for a regulatory submission, the consistency of the results for the primary and key secondary endpoints will be further explored by population and selected subgroups. In addition, different approaches will be applied for dealing with missing data.

9.7. SAMPLE SIZE CALCULATION

All sample size calculations were done in EAST 6.3.

9.7.1. Resolution of NASH

The following assumptions were made for the sample size calculation for resolution of NASH:

- α=0.01 two-sided
- Randomized patients with no response assessment at Week 72 will be counted as nonresponders
- Pooled variance
- Randomization ratio of 2:1 (elafibranor: placebo)
- 8% response in the control group
- 16.5% response in the elafibranor group.

The 8% response rate in the placebo group (calculated as the mean response rate based on the Phase II FLINT study[35] [subanalysis including only patients with stage 2 and stage 3 fibrosis or stage 1 fibrosis with diabetes, obesity or ALT ≥ 60 {associated with fibrosis progression}; placebo response rate 6.5%] and the GFT505-212-7 placebo data [11% response rate for patients with any stage fibrosis {F1; F2; F3} and 7% response rate for patients with only stage 2 and 3 fibrosis]). The 16.5% response rate in the elafibranor group is based on the Phase II GFT505-212-7 elafibranor data (calculated as the mean response

rate based on a 20% response rate for patients with any stage fibrosis ([F1; F2; F3] and 13% response rate for patients with only stage 2 and 3 fibrosis).

Based on these assumptions, a sample size of at least 1023 patients provides 90% power to show that elafibranor is superior to the placebo with respect to resolution of NASH without worsening of fibrosis.

9.7.2. Time to clinical event/death

The following assumptions were made for the sample size calculation for time to clinical event/death:

- 24 month enrollment (with an 18-month ramp up to as many as 200 patients per month)
- 72 month maximum follow-up
- α=0.04 two-sided
- Annual event rate of 7% for the placebo group
- Hazard ratio of 0.75 in favor of the elafibranor group
- 4% annual drop-out rate over 72 months
- Randomization ratio of 2:1 (elafibranor: placebo).

The 7% annual event rate in the placebo group is based on published literature on developing cirrhosis in patients with NASH and advanced fibrosis (F2-F3).[21,22,23,24,25] The rate of developing cirrhosis was estimated to be 7% (based on 8% per year in F3 patients and 6% per year in F2 patients). In a conservative approach, no additional event rate was added for other events than histological cirrhosis or cirrhosis decompensation events. An annual clinical event/death rate of 7% was thus defined for the composite of both these endpoints.

There is no long-term randomized clinical trial in a NASH population with moderate and severe liver fibrosis. In the 72-week FLINT trial, the total drop-out rate was 6.7%.[35] Therefore, we estimate an approximate annual drop-out rate of 4%. Based on these assumptions, 456 events are required to provide 80% power to show that elafibranor is superior to placebo with respect to time to clinical event/death. In order to obtain 456 events, at least 2022 patients will be required in the IIT.
The number of patients to be enrolled may be adjusted during the course of the study in a blinded manner to achieve the desired number of primary events. This will be accomplished using standard event forecasting methods (Anisimov, 2011).[40]

9.8. SAFETY ANALYSIS

Safety data (exposure, AEs, AESIs, clinical laboratory tests, vital signs, and ECGs) will be summarized by treatment group using descriptive statistics. The main summaries of safety will be based on the SS. Additional safety analysis will be based on the FSS and the exploratory F1 cohort.

Adverse events will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA). An overall summary of AEs will be provided. The number and percentage of patients reporting AEs will also be presented by MedDRA System Organ Class and preferred term. The AEs will be summarized

by worst severity and relationship to study drug. AESIs, serious AEs, and AEs leading to discontinuation will also be summarized. Narratives will be added for all SAEs and AESIs.

Clinical laboratory tests (hematology, chemistry, and urinalysis) recorded at each timepoint and change from baseline will be summarized by treatment group using descriptive statistics. Clinical laboratory values for each parameter will be assigned a classification according to whether the value is lower than, within, or higher than the reference range for that parameter. The values will then be summarized using shift tables to evaluate categorical changes from baseline to end of the 72 week treatment period with respect to reference ranges. The number and percentage of patients reporting markedly abnormal clinical laboratory values will also be summarized by treatment group.

Liver and kidney related laboratory tests including an assessment of DILI will also be summarized.

Vital signs recorded at each timepoint and change from baseline will be summarized by treatment group using descriptive statistics.

9.8.1. Surrogate endpoint analysis

The analysis of resolution of NASH without worsening of fibrosis will occur when at least the first 1023 randomized F2 and F3 patients complete 72 weeks of treatment or discontinue early from the study treatment. The null hypothesis will be tested at the two-sided 0.01 alpha level.

At this time, a snapshot of the database will be cleaned and locked for analysis and potential Subpart H or conditional approval submission. This analysis will be done by an unblinded team separate from the study team; the study team will not be unblinded until the final analysis at the end of follow-up. A Data integrity plan will be set-up to detail the blinding/unblinding process and address how data will be published in view of marketing authorization and how integrity of the trial will be protected.

The DSMB will periodically review safety data from the study to ensure the well-being of study participants. One dedicated meeting will also be held upon availability of the surrogate endpoint analysis results.
DSMB will be provided with data summaries that will include selected efficacy results so that the DSMB can assess the likely benefit-risk profile of elafibranor. These are not considered a formal interim analysis, and no type I error adjustments will be done for these reviews. Details will be in the DSMB Charter.

9.8.2. INTERIM ANALYSIS

An adaptive design interim analysis will be performed after 140 primary events (approx. 30% of the 456 required events) have been accrued. The interim analysis will be performed by an unblinded team separate from the study team. The Data Safety Monitory Board (DSMB) will review the interim analysis results and provide final recommendations regarding trial termination due to futility and adjustment of the target number of primary events. Details will be in the DSMB Charter and SAP.

10. DATA HANDLING AND RECORD KEEPING

10.1. CASE REPORT FORM AND SOURCE DOCUMENTS

A case report form (CRF) is required and should be completed for each screened patient. The completed eCRFs are the sole property of the Sponsor and should not be made available in any form to third parties, except for authorized Sponsor's representatives or appropriate regulatory authorities, without written permission from the Sponsor.

The Investigator will ensure that all data are entered promptly, legibly, completely, accurately and conform to source documents, in accordance with specific instructions accompanying the eCRFs designed specifically for this study. The CRF being used for this study is an electronic CRF that has been fully certified as being compliant with the FDA regulations at 21 Code of Federal Regulations (CFR) Part11.

All study required patient data generated during the study will be recorded in the eCRF, with the exception of SAE/AESI forms and SF-36 which will be collected via ePRO (which is then transferred to the electronic data capture). Patients will not be identified by name in the eCRF or on any study documents to be collected by the Sponsor (or designee), but will be identified by a patient number.

The Investigator will review and approve each completed eCRF; the Investigator's validation serving as attestation of the Investigator's responsibility for ensuring that all clinical and laboratory data entered in the eCRF are complete, accurate, and authentic.

Should a correction be made, the corrected information will be recorded in the eCRF by the authorized person and explained (if necessary). All corrected data will be tracked through an audittrail.

It is the Investigator's obligation to ensure documentation of all relevant data in the patient's medical file (medical history, concomitant diseases, patient identification number, date of informed consent, visit dates, administration of study medication, AEs [start and stop dates] and all concomitant medications [start and stop dates]). All data recorded in the eCRF will be documented by source data.

10.2. RETENTION OF RECORDS

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified.

The Investigator will be provided with a study file, which should be used to file the Investigator Brochure, protocol/amendments, drug accountability records, sample informed consent, staff curriculum vitae, correspondence with the IRB/IEC, Sponsor, and other study-related documents.

To enable evaluations and/or audits from regulatory authorities or the Sponsor, the Investigator agrees to keep records, including the identity of all participating patients, all original signed ICFs, copies of all eCRFs, source documents, and detailed records of treatment disposition.

The Investigator must retain the study documentation until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. However these documents should be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the Sponsor. All hospital records will be archived according to local regulation.

The Sponsor should be notified if the Investigator relocates, retires, or for any reason withdraws from the trial. The trial records must be transferred to an acceptable designee, such as another Investigator, another institution, or to the Sponsor.

11. QUALITY CONTROL AND QUALITY ASSURANCE

11.1. QUALITY CONTROL & MONITORING PROCEDURES

It is the responsibility of the Investigator to ensure that the study is conducted in accordance with the protocol, Good Clinical Practice (ICH topic E6), applicable regulatory requirements, and the current Declaration of Helsinki (APPENDIX I: World Medical Association Declaration of Helsinki) and that valid data are entered into the eCRFs.

To achieve this objective, the Study Monitor's duties are to aid the Investigator and, at the same time, the Sponsor in the maintenance of complete, legible, well-organized, and easily retrievable data.

Before enrolling any patients in this study, the Study Monitor will review the protocol, the brochure for clinical investigators, the eCRFs and instructions for their completion and return, the procedure for obtaining informed consent, and the procedure for reporting AEs and SAEs/AESIs with the Investigator. In addition, the Study Monitor will explain the Investigator's reporting responsibilities and all applicable regulations concerning the clinical evaluation of the study drug.

The Investigator will permit the representatives of Sponsor to monitor the study as frequently as the Sponsor deems is necessary to determine that data recording and protocol adherence are satisfactory. A Study Monitor from [redacted] Late Stage Development Services will be responsible for monitoring this clinical trial. To this end, the Study Monitor will visit the study site at suitable intervals and be in frequent contact through verbal and written communication. The eCRFs and related source documents, as well as drug accountability will be reviewed in detail by the monitor at each visit, in accordance with relevant SOPs and Good Clinical Practice (GCP; ICH topic E6) regulations. This includes results of tests performed as a requirement for participation in this study and any other medical records required to confirm information contained in the eCRFs, such as past medical history and secondary diagnoses.

A risk based monitoring strategy will be used for this study. Study monitoring strategy design will be based on overall study risk assessment. Individual site monitoring strategy design will be based on individual site risk assessment. On site monitoring will focus on source document verification of mandatory and critical data and source document review of critical processes, and will be supported by formal remote site monitoring activities. Centralized monitoring activities will review study data to assess changes in individual site risk and to identify emerging trends, risks and issues across sites, countries, regions, and the global study. Further details can be found in the Monitoring Plan.

It is essential that the Study Monitor has access to all documents (related to the study and the individual participants) at any time these are requested. In turn, the Study Monitor will adhere to all requirements for patient confidentiality as outlined in the ICF. The Investigator and Investigator's staff will be expected to cooperate with the Study Monitor, to be available during a portion of the Monitoring Visit to answer questions, and to provide any missing information.

All monitoring activities will be reported and archived in the Trial Master File.

11.2. ETHICAL PRINCIPLES

This protocol complies with the principles laid down by the 18th World Medical Assembly (Helsinki, 1964) and all applicable amendments laid down by the World Medical Assemblies (APPENDIX I: World Medical Association Declaration of Helsinki), and the GCP guideline.

This trial also complies with applicable local regulatory requirements and laws of each country in which the study is performed, as well as any applicable guidelines.

11.3. QUALITY ASSURANCE

For the purpose of ensuring compliance with the protocol, GCP and applicable regulatory requirements, the Investigator should permit auditing by the Sponsor and/or designee and inspection by applicable regulatory authorities. The Investigator agrees to allow the auditors/inspectors to have direct access to his/her study records for review, being understood that these personnel will adhere to all requirements for patient confidentiality, and as such will not disclose any personal identity or personal medical information.

As soon as the Investigator is notified of a future inspection by the Authorities, he/she will inform the Sponsor and authorize the Sponsor to participate at this inspection.

The confidentiality of the data verified and the anonymity of the patients should be respected during these inspections.

Clinical data associates from the Sponsor's representative will review the data for completeness and logical consistency. Additionally, the clinical data associates will use automated validation programs to help identify missing data, selected protocol violations, out of range data, and other data inconsistencies.
Requests for data clarification or correction will be electronically provided to the investigative site for resolution. Clinical data associates will assure that corrections have been applied properly.

12. ETHICS AND REGULATORY

12.1. INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE

The GCP guidelines and the US CFR Title 21 Section 56 (21 CFR 56) require that approval must be obtained from an Independent Ethics Committee (IRB/IEC) prior to participation of human patients in research studies. Prior to the study onset, the protocol, ICF, advertisements to be used for patient recruitment, and any other written information regarding this study to be provided to the patient or the patient's legally acceptable representative must be approved by the IRB/IEC. The Sponsor will supply relevant material for the Investigator to submit to the IRB/IEC for the protocol's review and approval. Verification of the IRB's unconditional approval of the protocol and the written ICF statement will be transmitted to the Investigator. Documentation of the relevant IRB/IEC approval and of the IRB/IEC compliance with GCP guideline will be maintained by the site and will be available for review by the Sponsor or its designee or by the authorized members of regulatory agencies.

The Applicant must supply the Sponsor with written documentation of the initial favorable opinion of the clinical research before the start of the trial.

The study will not commence until favorable opinion has been obtained from the appropriate IRB/IEC.

If any alterations, other than changes of administrative nature only, are made to the study protocol, a formal protocol amendment will be issued. The IRB/IEC will be informed by the Investigator of subsequent protocol amendments and of SUSARs. Approval for protocol amendments will be transmitted in writing to the Investigator.

The amendment will not be implemented until IRB/IEC approval, except in cases where immediate implementation is necessary to eliminate or prevent imminent hazard to the patients. A protocol change intended to eliminate an apparent immediate hazard must be documented in an amendment, reported to the IRC/IEC within 5 working days, and submitted to the appropriate regulatory agencies in the required time frame.

If requested, the Investigator will permit audits by the IRB/IEC and regulatory inspections by providing direct access to source data/documents.

The Investigator will provide the IRB/IEC with progress reports at appropriate intervals (not to exceed 1 year) and a Study Progress Report following the completion, termination, or discontinuation of the Investigator's participation in the study.

12.2. COMPETENT AUTHORITY

In the same way as for IRB/IEC (see Section 12.1), when required by national regulation, approval from Competent Authorities (CA) should be granted before the beginning of the study. If applicable, Amendments will also be submitted to CA for approval.

12.3. PATIENT INFORMATION AND CONSENT

Written informed consent for the study will be obtained from each patient before protocol-specific procedures are carried out. The ICF used by the Investigator for obtaining the patient's Informed Consent must be reviewed and approved by the Sponsor prior to submission to the appropriate ethics committee (IRB/IEC). The ICF will be approved (along with the protocol) by the IRB/IEC.

In the case of any exploratory substudies, specific study documents will be prepared and IRB/IEC and authority approvals shall be obtained when applicable.

The Investigator or a person designated by the Investigator (according to applicable regulatory requirements), will explain the nature of the study and the action of the test product. The patients will be informed that participation is voluntary and that they can withdraw from the study at any time. In accordance with 21 CFR 50, the informed consent process shall be documented by the use of a written ICF approved by the designated IRB/IEC and will be signed and personally dated by the patient or by the patient's legally acceptable representative and by the person who conducted the informed consent discussion prior to protocol-specific procedures being performed. A separate consent form will be obtained for optional genetic and biomarker samples to be stored in the blood bank.

The Investigator must maintain the original, dated and signed ICF. A copy of the signed ICF must be given to the patient.

12.4. PATIENT CONFIDENTIALITY

The Sponsor will affirm and uphold the principle of the patient's right to protection against the invasion of privacy. Throughout this study and any subsequent data analyses, all data will be identified only by protocol number and patient number.

All unpublished information that the Sponsor gives to the Investigator shall be kept confidential and shall not be published or disclosed to a third party without the prior written consent of the Sponsor.

When the Sponsor generates reports for presentations to regulatory agencies, one or more of the Investigators who has/have contributed significantly to the study will be asked to endorse the final report. The endorsement is required by some regulatory agencies.

The Investigator shall not make a patent application based on the results of this study and shall not assist any third party in making such an application without the written authorization of the Sponsor unless otherwise specified in the CSA.

12.5. DEFINITION OF THE END OF THE RESEARCH

End of the research corresponds to the last observation for the last patient participating in the research.

13. FINANCING AND INSURANCE

13.1. FINANCIAL ISSUES

Financial contracts will be signed between the Sponsor and the Investigator/Institution before initiation of the study.

13.2. INSURANCE AND PATIENT INJURY

The patients taking part in the trial will be covered by the insurance taken by the Sponsor for this trial, if they were to suffer any prejudice as a result of taking part in the trial.

In general, if a patient is injured as a direct result of the study drug, the Sponsor will pay for reasonable and necessary medical treatment for the injury, to the extent the expenses are not covered by the patient's medical insurance, a government program, or other responsible third party. If laws or regulations of the locality in which the trial is taking place require additional payment of expenses, the Sponsor shall comply with such law or regulation.

The Sponsor certifies to have taken out an insurance policy to cover the financial consequences of its civil liability and that of everyone involved in the research, and notably that of the Investigators and their colleagues with regard to any accidents or damage concerning the administration of the drug or paraclinical examinations directly linked to the performance of the trial.

14. STUDY RESULTS AND PUBLICATION POLICY

14.1. STUDY REPORT

The final report will be written in ENGLISH upon completion of study and statistical analysis according to ICH E3 guideline. The report or part of it must be submitted to relevant authorities if applicable.

[redacted] will prepare an integrated clinical and safety report. Prior to issuing the final CSR, [redacted] will prepare a draft report for approval by the Sponsor. The report will be in accordance with the ICH E3 Guideline for Industry: Structure and Content of CSRs. The draft report will be submitted for Quality Assurance audit, the findings of which will be incorporated into the final version.

An electronic copy of the final CSR will be made available to the Sponsor. The study report will be provided in PDF and MS Word formats unless agreed otherwise by [redacted] Reports requiring specialized Sponsor formats/alternative computer software packages may be possible on request from the Sponsor but may involve extra time and cost. Electronic datasets will also be provided to the Sponsor on issuance of the final report.

After review by the Sponsor, a final CSR will be submitted to the Sponsor which incorporates the Sponsor's comments.

14.2. CONFIDENTIALITY AND OWNERSHIP OF DATA, USE OF THE STUDY RESULTS AND PUBLICATION

All materials, information (oral or written), and unpublished documentation provided to the Investigators (or any company/institution acting on their behalf), including this protocol, the patient CRFs, and the Investigator's Brochure, are the exclusive property of the Sponsor and may not be published, given, or disclosed, either in part or in whole, by the Investigator or by any person under his/her authority to any third party without the prior express consent of the Sponsor.

However, the submission of this protocol and other necessary documentation to the ethics committee (IRB/IEC) and the Competent Authority is expressly permitted, their members having the same obligation of confidentiality.

The Investigator shall consider all information, results, discoveries, records (accumulated, acquired, or deduced) in the course of the study, other than that information to be disclosed by law, as confidential and shall not disclose any such results, discoveries, or records to any third party without the Sponsor's prior written consent.

The Sponsor retains exclusive ownership of all data, results, reports, findings, discoveries, and any other information collected during this study. Therefore, the Sponsor reserves the right to use the data from the present study, either in the form of Case Report Forms (or copies of these), or in the form of a report,

with or without comments and with or without analysis, in order to submit them to the Health Authorities of any country.

When the Sponsor generates reports for presentations to regulatory agencies, one or more of the Investigators who has/have contributed significantly to the study will be asked to endorse the final report. The endorsement is required by some regulatory agencies.

Furthermore, in the event that the study generates patentable results, the Investigator (or entity acting on his/her behalf according to local requirements) shall refrain from filing patent application(s) on such results, which will be filed by the Sponsor or its designees in its own name and at its expense.

Clinical study will be registered on the open access website http://www.clinicaltrials.gov before the screening of the first patient in the study.

It is the policy of the Sponsor to encourage the presentation and/or publication of the results of their studies, using only clean, checked, and validated data in order to ensure the accuracy of the results.

The publication of study results will be agreed between the Sponsor and the Investigators.

At least 45 days in advance of proposed submission, the Investigator should forward a copy of the manuscript or abstract for review by the Sponsor, and, if necessary, delay publication or communication for a limited time in order to protect the confidentiality or proprietary nature of any information contained therein. The Sponsor may also request that the Sponsor's name and/or names of one or several of its employees appear or not appear in such publication.

15. REFERENCES LIST

1. Day CP, James OF. Steatohepatitis: a tale of two "hits"? *Gastroenterology*. 1998;114:842-845.
2. Jou J, Choi SS, Diehl AM. Mechanisms of disease progression in nonalcoholic fatty liver disease.
   Semin Liver Dis. 2008;28: 370-379.
3. Edmison J, McCullough AJ. Pathogenesis of nonalcoholic steatohepatitis: human data. *Clin Liver Dis*. 2007;11:75-104.
4. Browning JD, Horton JD. Molecular mediators of hepatic steatosis and liver injury. *J Clin Invest*. 2004;114:147-152.
5. Ikejima K, Honda H, Yoshikawa M, et al. Leptin augments inflammatory and profibrogenic responses in the murine liver induced by hepatotoxic chemicals. *Hepatology*. 2001;34: 288-297.
6. Poniachik J, Santibanez C, Haim D, et al. Enhancement in liver nuclear factor-kb (NF-KB) and activator protein 1 (AP-1) DNA binding in obese patients with nonalcoholic fatty liver disease. The 43rd Annual Meeting of the European Association for the Study of the Liver. Milan, Italy, 2008.
7. Yamauchi T, Kamon J, Minokoshi Y, et al. Adiponectin stimulates glucose utilization and fatty- acid oxidation by activating AMP-activated protein kinase. *Nat Med*. 2002;8(11):1288-95. Epub 2002 Oct 7.
8. Targher G, Bertolini L, Rodella S, et al. Associations between plasma adiponectin concentrations and liver histology in patients with nonalcoholic fatty liver disease. *Clin Endocrinol (Oxf).* 2006;64:679-683.
9. Xu H, Barnes G, Yang Q, et al. Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance. *J Clin Invest*. 2003;112(12):1821-1830.
10. Pessayre D, Fromenty B, Mansouri A. Mitochondrial injury in steatohepatitis. *Eur J Gastroenterol Hepatol*. 2004;16:1095-1105.
11. Crespo J, Cayon A, Fernandez-Gil P, et al. Gene expression of tumor necrosis factor alpha and TNF-receptors, p55 and p75, in nonalcoholic steatohepatitis patients. *Hepatology*. 2001;34:1158–1163.
12. Hotamisligil GS, Arner P, Caro JF, et al. Increased adipose tissue expression of tumor necrosis factor-alpha in human obesity and insulin resistance. *J Clin Invest.* 1995;95:2409-2415.
13. Ramalho RM, Cortez-Pinto H, Castro RE, et al. Apoptosis and Bcl-2 expression in the livers of patients with steatohepatitis*. Eur J Gastroenterol Hepatol*. 2006;18:21-29.
14. Laurin J, Lindor KD, Crippin JS, et al. Ursodeoxycholic acid or clofibrate in the treatment of nonalcohol-induced steatohepatitis: a pilot study. *Hepatology*. 1996;23(6):1464-1467.
15. Shan W, Nicol CJ, Bility MT, et al. Peroxisome proliferator-activated receptor-beta/delta protects against chemically induced liver toxicity in mice, *Hepatology*. 2008;47(1):225-235.

16. Risérus U, Sprecher D, Johnson T, et al. Activation of peroxisome proliferator-activated receptor (PPAR) delta promotes reversal of multiple metabolic abnormalities, reduces oxidative stress, and increases fatty acid oxidation in moderately obese men. *Diabetes*. 2008;57(2):332-339. Epub 2007 Nov 16.
17. Kang K, Reilly SM, Karabacak V, et al. Adipocyte-derived TH2 cytokines and myeloid PPAR delta regultate macrophage polarization and insulin sensitivity. *Cell Metab.* 2008;7:485-495.
18. Odegaard JI, Ricardo-Gonzalex RR, Red Eagle A et al. Alternative M2 activation of Kupffer cells by PPARδ ameliorates obesity induced insulin resistance. *Cell Metab*. 2008;7:496-507.
19. Cattley RC, Deluca j, Elcombe C, et al. Do peroxisome proliferating compounds pose a hepatocarcinogenic hazard to humans? *Regul Toxicol Pharmacol*. 2008;27(1 Pt 1):47-60.
20. Musso G, Gambino R, Cassader M, Pagano G . Meta-analysis: natural history of nonalcoholic fatty liver disease (NAFLD) and diagnostic accuracy of non-invasive tests for liver disease severity. *Ann Med*. 2011;43(8):617-649.
21. Ekstedt M, Franzen LE, Mathiesen UL, et al. Long-term follow-up of patients with NAFLD and elevated liver enzymes. *Hepatology.* 2006;44(4):865-873.
22. Angulo P, Kleiner DE, Dam-Larsen S, et al. Liver Fibrosis, but No Other Histologic Features, Is Associated With Long-term Outcomes of Patients With Nonalcoholic Fatty Liver Disease. *Gastroenterology.* 2015;149(2):389-397 e310.
23. Argo CK, Northup PG, Al-Osaimi AM, Caldwell SH . Systematic review of risk factors for fibrosis progression in nonalcoholic steatohepatitis. *J Hepatol*. 2009;51(2):371-379.
24. Pagadala MR, McCullough AJ. The relevance of liver histology to predicting clinically meaningful outcomes in nonalcoholic steatohepatitis. *Clin Liver Dis* 2012;16(3):487-504.
25. Singh S, Allen AM, Wang Z, Prokop LJ, Murad MH, Loomba R. Fibrosis progression in nonalcoholic fatty liver vs nonalcoholic steatohepatitis: a systematic review and meta-analysis of paired-biopsy studies. *Clin Gastroenterol Hepatol.* 2015;13(4):643-654.
26. Hashimoto E, Tokushige K. Prevalence, gender, ethnic variations, and progression of NASH. *J Gastroenterol.* 2011;46(supplement 1):63-69.
27. Younossi ZM, Stepanova M, Rafiq N, et al. Pathologic criteria for nonalcoholic steatohepatitis: interprotocol agreement and ability to predict liver-related mortality. *Hepatology.* 2011;53(6):1874-1882.
28. Ratziu V, de Ledinghen V, Oberti F, et al. A randomized controlled trial of high-dose ursodesoxycholic acid for nonalcoholic steatohepatitis. *J Hepatol.* 2011;54(5):1011-1019.
29. Sanyal AJ, Brunt EM, Kleiner DE, et al. Endpoints and clinical trial design for nonalcoholic steatohepatitis. *Hepatology*. 2011;54:344-353.
30. Sanyal AJ, Friedman SL, McCullough AJ, et al. Challenges and opportunities in drug and biomarker development for nonalcoholic steatohepatitis: findings and recommendations. *Hepatology.* 2015;61(4):1392-1405.
31. McPherson S, Hardy T, Henderson E, et al. Evidence of NAFLD progression from steatosis to fibrosing-steatohepatitis using paired biopsies: implications for prognosis and clinical

management. *J Hepatol*. 2015;62(5):1148-1155.

32. Dunn W, Xu R, Wingard DL, et al. Suspected nonalcoholic fatty liver disease and mortality risk in a population-based cohort study. *Am J Gastroenterol.* 2008;103(9):2263-2271.
33. Rafiq N, Bai C, Fang Y, et al. Long-term follow-up of patients with nonalcoholic fatty liver. *Clin Gastroenterol Hepatol.* 2009;7(2):234-328.
34. Clinical Trial Facilitation Group (2014). Recommendations related to contraception and pregnancy testing in clinical trials. Available at: http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf
35. Neuschwander-Tetri BA, Loomba R, Sanyal AJ, et al. Farnesoid X nuclear receptor ligand obeticholic acid for non-cirrhotic, nonalcoholic steatohepatitis (FLINT): a multicentre, randomised, placebo-controlled trial. *Lancet*. 2015;385(9972):956-965.
36. Ge, M., Durham, L. K., Meyer, R. D., Xie, W., & Thomas, N. (2011). Covariate-adjusted difference in proportions from clinical trials using logistic regression and weighted risk differences. *Drug Information Journal*, *45*(4), 481-493.
37. Saville RS and Koch G. Estimating Covariate-Adjusted Log Hazard Ratios in Randomized Clinical Trials Using Cox Proportional Hazards Models and Nonparametric Randomization Based Analysis of Covariance. Journal of Biopharmaceutical Statistics. 2013 23: 477-490.
38. Dmitrienko, A., Tamhane, A.C. Mixtures of multiple testing procedures for gatekeeping applications in clinical trials. Statistics in Medicine. 2011 30: 1473-1488.
39. Dmitrienko, A., Tamhane, A.C. General theory of mixture procedures for gatekeeping. Biometrical Journal. 2013 55: 402-419.
40. Anisimov, V. Predictive event modelling in multicentre clinical trials with waiting time to response. Pharmaceutical Statistics. 2011; 10, 517-522.
41. Zink RC and Koch G. NParCov3: A SAS/IML Macro for Nonparametric Randomization-Base Analysis of Covariance. Journal of Statistical Software. 2012 July 50:3.

16. Appendices

16.1. APPENDIX I: WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964
and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words,

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"The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by

individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and

standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

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27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain

for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made

publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

16.2. APPENDIX II: ADEQUATE DIET AND LIFESTYLE RECOMMENDATIONS

Essential Components of Therapeutic Lifestyle Changes (TLC)

Component	Recommendation
LDL-raising nutrients	
Saturated fats*	Less than 7% of total calories
Dietary cholesterol	Less than 200 mg/day
Therapeutic options for LDL lowering	
Plant stanols/sterols	2 grams per day
Increased viscous (soluble) fiber	10–25 grams per day
Total calories (energy)	Adjust total caloric intake to maintain desirable body weight/prevent weight gain
Physical activity	Include enough moderate exercise to expend at least 200 kcal per day

* *Trans* fatty acids are another LDL-raising fat that should be kept at a low intake.

Macronutrient Recommendations for the TLC Diet

Component	Recommendation
Polyunsaturated fat	Up to 10% of total calories
Monounsaturated fat	Up to 20% of total calories
Total fat	25–35% of total calories*
Carbohydrate†	50–60% of total calories*
Dietary fiber	20–30 grams per day
Protein	Approximately 15% of total calories

* ATP III allows an increase of total fat to 35 percent of total calories and a reduction in carbohydrate to 50 percent for persons with the metabolic syndrome. Any increase in fat intake should be in the form of either polyunsaturated or monounsaturated fat.
† Carbohydrate should derive predominantly from foods rich in complex carbohydrates including grains—especially whole grains—fruits, and vegetables.

16.3. APPENDIX III: PERMITTED/NON-PERMITTED MEDICATION

Table I: NON-PERMITTED MEDICATION AND CONDITION

Medications	**When**
Same pharmacological class (PPAR agonists)	
Thiazoledinediones (glitazones [pioglitazone and rosiglitazone])	From 6 months prior to diagnostic liver biopsy* up to end of study treatment (EOT) Visit
Fibrates	From 2 months prior to Randomization up to EOT Visit
Medication that may induce steatosis/steatohepatitis	
Corticosteroids (parenteral & oral chronic administration)	From 30 days prior to first Screening Visit up to EOT Visit
Amiodarone	
Tamoxifen	
Methotrexate	
Medication that may interact with absorption, metabolism, etc	
Indomethacin	From Randomization up to EOT Visit

* Given the potential effect on diagnostic liver biopsy of patients previously treated by glitazones

Table II: PERMITTED MEDICATION AND CONDITION

Medications	When
Antidiabetic therapy	
GLP-1 agonist	Dose stability required in the 6 months prior to the diagnostic liver biopsy No qualitative change (i.e., no initiation of a new drug) from at least 6 months prior to the diagnostic liver biopsy up to 72-week of treatment (V7). Dose changes after randomization should be avoided
All other ATD therapy (insulin, sulfonylureas, metformin, gliptins)	No qualitative change (i.e., no initiation of a new drug) from at least 6 months prior to the diagnostic liver biopsy and up to Randomization (Dose changes are allowed). Dose changes after randomization are allowed.
SGLT2-inhibitors	No qualitative change (i.e., no implementation of a new drug) from at least 6 months prior to the diagnostic liver biopsy up to 72-weeks of treatment (V7). Dose changes after randomization should be avoided.
Lipid lowering therapy	
Statins	Dose stability required from at least 2 months prior to Screening. Dose changes are allowed after Randomization if judged necessary by the physician
Ezetimibe	
Other nonfibrate lipid lowering therapies	
Others	
Vitamin E >400 IU/day	Dose stability required from at least 6 months prior to the diagnostic liver biopsy. Dose changes should be avoided up to EOT
PUFAs >2 g/day	
Ursodeoxycholic acid	

Abbreviations: ATD = autoimmune thyroid disease; EOT = end of study treatment; GLP-1 =glucagon-like peptide 1; PUFA = polyunsaturated fatty acids; SGLT2 = sodium/glucose cotransporter 2.

16.4. APPENDIX IV: ALCOHOL COMPARISON TABLE

Alcohol type	Alcohol by volume (ABV)	Volume		Amount of alcohol	
		Fluid ounce	mL	Units 2	grams
Beer	3.5%	12	350	0.7	9.8
Beer	5%	12	350	1	14
Cider	7%	12	350	1.4	19.6
Distilled spirits or liquor 1	40%	1.5	45	1	14
Wine	12%	5	150	1	14

1. e.g., gin, rum, vodka, whiskey.

Units calculated using the cleave Books calculator for units of drink, using the US definition of 1 unit of alcohol as 17.7 mL (14.0 g) of pure alcohol (http://www.cleavebooks.co.uk/scol/ccalcoh3.htm).

16.5. APPENDIX V: PRODUCT CARTON AND WALLET LABELING

	Carton	Wallet
Protocol number	X	X
Sponsor details	X	X
Site number	X	-
Subject ID	X	X
Kit number	X	X
Visit number	X	-
Lot number	X	X
Expiry date	X	X
Contents	X	X
Route of administration	X	X
Administration instructions	X	X
"For Clinical Trial Use only."	X	X
"Keep out of reach of Children."	X	X
Storage details	X	X
Instructions for product and package return at next visit	X	X