CLINICAL PROTOCOL – PHASE 2A

PROTOCOL N° GFT505E-218-1

IND NUMBER: 115028

AMENDMENT 3: FINAL 4.0 - RELEASE DATE: 20 APRIL2020

Supersedes previous Version 3.0 - Release date 21 February 2020

An Open Label, Randomized, Multicenter Study to Assess the Pharmacokinetic and Pharmacodynamic Profile and the Safety and Tolerability of Two Dose Levels of Elafibranor (80 mg and 120 mg) in Children and Adolescents, 8 to 17 Years of Age, with Nonalcoholic Steatohepatitis (NASH)

Sponsor	GENFIT	Parc Eurasanté 885, avenue Eugène Avinée 59120 LOOS France
Represented by:	PPD , MD PPD	Phone: PPD E-mail:PPD

[redacted]

SIGNATURE PAGE

Protocol Title:	An Open Label, Randomized, Multicenter Study to Assess the Pharmacokinetic and Pharmacodynamic Profile and the Safety and Tolerability of Two Dose Levels of Elafibranor (80 mg and 120 mg) in Children and Adolescents, 8 to 17 Years of Age, with Nonalcoholic Steatohepatitis (NASH)
Protocol Code:	GFT505E-218-1
IND Number:	115028
Version:	4.0
Release Date:	20 April 2020

On behalf of (the Sponsor):

GENFIT
Parc Eurasanté
885, avenue Eugène Avinée
59120 LOOS – France

PPD , MD

Print Name

Signature

Date

CLINICAL STUDY PROTOCOL - INVESTIGATOR SIGNATURE PAGE

Protocol Title:	An Open Label, Randomized, Multicenter Study to Assess the Pharmacokinetic and Pharmacodynamic Profile and the Safety and Tolerability of Two Dose Levels of Elafibranor (80 mg and 120 mg) in Children and Adolescents, 8 to 17 Years of Age, with Nonalcoholic Steatohepatitis (NASH)
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Clinical Phase:	2a
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Sponsor:	GENFIT Parc Eurasanté, 885 avenue Eugène Avinée, 59120 Loos – France

I have read this protocol, agree that the protocol contains all the information necessary to conduct the study and with my signature confirm that I'll conduct the study according to it and that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

Investigator Name: _____

Institution Name: _____

Institution Address: _____

_____

_____

_____ _____

Signature Date

STUDY CONTACTS

PROTOCOL N°: GFT505E-218-1/ IND N° 115028

Sponsor	GENFIT PPD , MD PPD	Parc Eurasanté 885, avenue Eugène Avinée 59120 LOOS – France Phone: PPD E-Mail: PPD
CRO for Monitoring and PK Parameter Analysis	PPD	
CRO for Data-Management & Statistics		
Pharmaco-vigilance		
Study Drug Supplier		
Central Laboratory		
CRO for PK Testing		

Summary of changes to the protocol:

Section	New Text (additions in bold; deletions in strikethrough)
Section 5.2.1	**Due to the COVID-19 crisis, the screening window (i.e., the time from the signing of consent / screening visit 1 to randomization) can be extended to be up to 8 weeks if no onsite visit is possible earlier.**
Section 5.3.3	• 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 5.2.2.** **These solutions can be applied after Medical Monitor approval and depending on the investigator's judgment of each case and the patient/parent(s)'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 and parent(s) to check whether they agree 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.** ***5.3.3.1 Safety and drug compliance procedures*** **The following procedures will be performed if applicable for the visit via either a phone contact, or, if safe and possible, a direct visit to the patient:** • **Check for AEs** • **Collection of any lifestyle modifications** • **Check concomitant/prior medication** • **Check of compliance (review of dosing diary with the patient/parent(s))** • **Physical examination if possible with a direct visit to the patient or using video (described in Section 6.2.1)** • **Record vital signs, waist circumference and weight if possible with a direct visit to the patient (described in Section 6.2.1 and Section 6.2.2)** ***5.3.3.2 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 and biochemistry testing. **If a direct visit to the patient is safe and possible, the appropriate lab parameters corresponding to the on-site study visit will be collected.** ***5.3.3.3 Delivery of study treatment to the patient*** **The study treatment can be shipped to the patient or delivered directly to the patient by the site study staff if safe and possible as per the site procedure.** **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 7.7 and Section 7.8 once brought to the study site/study pharmacy.** ***5.3.3.4 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.**

CLINICAL TRIAL SYNOPSIS

Sponsor	Study Drug	Protocol Number
GENFIT	Elafibranor (GFT505)	GFT505E-218-1

Title of the study

An Open Label, Randomized, Multicenter Study to Assess the Pharmacokinetic and Pharmacodynamic Profile and the Safety and Tolerability of Two Dose Levels of Elafibranor (80 mg and 120 mg) in Children and Adolescents, 8 to 17 Years of Age, with Nonalcoholic Steatohepatitis (NASH)

Phase: 2a

Indication: Treatment of Nonalcoholic Steatohepatitis (NASH)

Study Design and dose levels

This study is an open-label, randomized, multicenter, sequential cohort study that will assess the pharmacokinetics (PK), safety, and pharmacodynamics (PD) and explore the relationship between PK and PD response following 12 weeks of once daily oral administration of elafibranor at doses of 80 mg and 120 mg in children and adolescents, 8 to 17 years of age (inclusive), with histologically confirmed (historical biopsy) nonalcoholic steatohepatitis (NASH). The target population will include patients with NASH with and without fibrosis. Of the 20 patients that will be enrolled and dosed with elafibranor, at least 4 patients ≥12 to ≤17 years of age, and at least 2 patients ≥8 to ≤11 years of age, will have significant fibrosis [*i.e.*, fibrosis stage 2 or 3]).

Two patient cohorts will be dosed sequentially. Cohort 1 will consist of approximately 12 patients who are ≥12 to ≤17 years of age and will be enrolled first. Once 10 (80%) patients in cohort 1 have been evaluated for PK and safety through Visit 4 by the Data Safety Monitoring Board (DSMB), and if agreed upon by the DSMB, enrollment will be open to patients ≥8 to ≤11 years of age. Cohort 2 will consist of approximately 8 patients who are ≥8 to ≤11 years of age.

Potential patients will be screened within 28 days (Day -28 [Week -4] to Day -7 [Week -1]) prior to Day 1. Day 1 will include randomization and dosing with study drug. After signing the informed consent form (ICF) (parent/legal guardian) and the assent (patient) documents, patients will undergo screening procedures to confirm study eligibility. The patient (and parent/legal guardian) will be given counselling regarding a diet and exercise regimen to be maintained starting from the screening visit.

Eligible patients will return to the clinic on Day 1. Baseline evaluations[1] will be obtained prior to study drug administration. Patients will be randomized (1:1) to receive either 80 mg or 120 mg once daily for 12 weeks. The patient (and parent/legal guardian) will again be counselled on dietary and exercise regimen requirements that will be maintained throughout the study period. Patients will be dispensed a 1-month supply of study drug and dosing diary and will be scheduled for their next visit on Day 15 (± 2 days) for safety evaluations and compliance check[1].

The patient will return on Day 29 (± 2 days)/Week 4 for safety, PD (biological laboratory assessments), PK assessments, and compliance check[1]. A 1-month supply of study drug and dosing diary will be dispensed. The patient will return the following day for collection of the 24-hour (±10 minutes) post-dose sample (prior to the next daily dose). The patient will return to the clinic on Day 57 (± 2 days)/Week 8 and Day 85 (± 2 days)/Week 12, for safety, PD (biological laboratory assessments) and compliance evaluations. On Day 57 (± 2 days)/Week 8, in addition to safety and PD, a 1-month supply of study drug and dosing diary will be dispensed. At the End of Treatment (EOT) visit, Day 85 (± 2 days)/Week 12, quality of life will be assessed, the final PK sample will be collected, and unused study drug and completed diary will be collected. A final safety evaluation will be conducted at the End of Study (EOS) visit, Day 113 (± 2 days)/Week 16.

[1]Refer to General Study Assessment Schedule and Section 5 – Trial Procedures for detailed procedure listings.

Route of Administration: Oral

Dose Levels: Two dose levels will be evaluated in this study; 80 mg administered once daily for 12 weeks and 120 mg administered once daily for 12 weeks.

Study Objectives

Primary Objective

- To assess the pharmacokinetics of elafibranor and its active metabolite GFT1007, following once daily oral administration of two dose levels of elafibranor (80 mg and 120 mg) to children and adolescents, 8 to 17 years of age (inclusive).

Secondary Objectives

Pharmacodynamic

- To assess changes in serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), and alkaline phosphatase (ALP) and other liver markers;
- To assess changes in markers of glucose homeostasis (homeostatic model assessment for insulin resistance (HOMA-IR) and fasting insulin);
- To assess changes in serum lipid parameters;
- To assess changes in body weight and Body Mass Index (BMI) z-score;
- To assess changes in waist circumference;
- To assess changes in inflammatory markers;
- To assess the change in the pediatric quality of life (PedsQL™) score as completed by the child/adolescent and the parent/legal guardian.

Safety

- To assess the safety and tolerability profile of two dose levels of elafibranor (80 mg and 120 mg) in children and adolescents, 8 through 17 years of age.

Exploratory Objectives

- CCI [redacted]

Patient Population

Children and adolescents, 8 to 17 years of age (inclusive), with histologically confirmed (historical biopsy) NASH. The target population will include patients with NASH, with and without fibrosis. At least 4 patients ≥12 to ≤17 years of age, and at least 2 patients ≥8 to ≤11 years of age, will have history of significant fibrosis (*i.e.*, fibrosis stage 2 or 3).

Randomization

Number of Randomized Patients (planned): A total of 20 patients will be enrolled across the two cohorts.

- Cohort 1: ≥12 to ≤17 years of age. A total of approximately 12 patients will be randomized in this cohort.
- Cohort 2: ≥8 to ≤11 years of age. A total of approximately 8 patients will be randomized in this cohort. Enrollment in this cohort will not start until 80% of the patients in cohort 1 have been evaluated through Visit 4 by the DSMB.

Patients will be randomized 1:1 to receive either dose (80 or 120 mg).

Considering that at least 4 patients ≥12 to ≤17 years of age and at least 2 patients ≥8 to ≤11 years of age with fibrosis stage 2 or 3 will be enrolled and to achieve balance between dosing groups according to the fibrosis severity, randomization will be stratified within each cohort based upon the patient's historical (liver biopsy used for study qualification) fibrosis severity stage (stratum 1: fibrosis stage 0 to 1 and stratum 2: fibrosis stage 2 to 3).

Number of participating centres (planned): Two (2)

Number of participating countries: One (1) United States (US)

Study Duration Per Patient

Each patient will participate in the study for up to approximately 20 weeks (screening through final follow-up visit).

Study Schedule

- Screening:
  - Screening Visit 1 Week -4 to Week -1 (SV1): Day -28 to Day -7
  - Screening Visit 2 Week -1 (SV2): Day -5 (±2 days) (telephone contact only)
- Randomization and Treatment: Day 1 to Day 85 (±2 days)
  - Visit 1 Week 0 (Randomization): Day 1
  - Visit 2 Week 2: Day 15 (±2 days)
  - Visit 3 Week 4: Day 29 (±2 days)
  - Visit 4 Week 4: Day 30 (24h PK sample collection)
  - Visit 5 Week 8: Day 57 (±2 days)
  - Visit 6 Week 12 (EOT): Day 85 (±2 days)
- Follow-up: Day 86 to Day 113 (±2 days) (Week 12 to Week 16)
  - Visit 7 Week 16 (EOS): Day 113 (±2 days)

Inclusion Criteria

For a study patient to be evaluated for study participation:

1. Parent(s)/Legal Guardian(s) must provide written Informed Consent (including the Health Insurance Portability and Accountability Act [HIPAA]) prior to the conduct of any study related procedures to permit participation of a minor in a clinical research study in accordance with federal and local laws. Additionally, assent from a minor child will be obtained in accordance with federal and local laws as well as in compliance with the recommendations of the approving Institutional Review Board (IRB)/Independent Ethics Committee (IEC).

Study patients will be eligible for inclusion in the study if they meet all the following criteria at Screening and up to the time of Randomization (Visit 1) as applicable:

2. Are male or female between 8 and 17 years of age (inclusive) at the time of Screening Visit 1 (when consent for study participation is given) and at the time of Randomization (Visit 1).
3. Diagnosis of non-alcoholic steatohepatitis (NASH) confirmed by histological evaluation (with or without fibrosis) from a liver biopsy obtained within 24 months prior to Randomization (Visit 1/Day 1).
4. Has adhered to a minimum of 3 months of lifestyle modification to treat NASH, prior to Screening (SV1), and agrees to adhere to lifestyle modifications (diet and exercise) throughout the study period (Screening through final visit [Visit 7/Day 113]).
5. Has an alanine aminotransferase (ALT) level greater than (>) 50 IU/L, at Screening (SV1).
6. Has a Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) ≥ 5, at Screening (SV1).
7. Has a Body Mass Index z-score (BMI z-score) (also referred to as BMI-for-age percentile) greater than or equal to (≥) 85th percentile for age and gender at Screening (SV1).
8. Has a Hemoglobin A1C (HbA1c) less than or equal to (≤) 8.5%. If the patient has Type 2 diabetes and is taking anti-diabetic therapy (e.g., metformin or insulin), treatment must have been started at least 3 months prior to Screening (SV1) and the dose must be stable for at least 3 months prior to Screening (SV1) and should remain stable through Randomization (Visit 1/Day 1).
9. If patient is taking medications or supplements to treat non-alcoholic fatty liver disease/non-alcoholic steatohepatitis (NAFLD/NASH) (Vitamin E, ursodeoxycholic acid, polyunsaturated fatty acids [PUFAs]), the dose must be stable for at least 3 months prior to Screening Visit 1 and should remain stable through Randomization (V1/Day 1) and planned to remain stable through EOS.
10. Sexually active female participants of childbearing potential must agree to utilize a highly effective method of contraception per the Clinical Trial Facilitation Group (CTFG) Guidelines (refer to Appendix IV), from Screening through 30 days after the last dose of study drug (1 month after the end of treatment (EOT), and agree to monthly pregnancy testing during the study up to and including EOS.
11. The Parent(s)/Legal guardian(s) and study patient are willing and able to follow all study-related procedures, including but not limited to daily study drug administration, pharmacokinetic (PK) sampling, be willing and able to return to the study clinic for study visits and be accessible by phone or e-mail for study related communications.
12. Patient agrees not to consume alcohol or use illicit drugs during the study up to and including EOS.

Exclusion Criteria

A study patient will be excluded from the study if they meet any of the following criteria at Screening (SV1) or prior to Randomization (Visit 1/Day 1):

1. Has history of bariatric surgery or planned surgery during the study period.
2. Has known history of heart disease.
3. Has uncontrolled hypertension evidenced by sustained elevation in systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg despite treatment with antihypertensive therapy, prior to Randomization (Visit 1/Day 1).
4. Has a known history of Type 1 diabetes.
5. Has a known history of acquired immunodeficiency syndrome or positive screening for human immunodeficiency virus (HIV) antibodies at Screening Visit 1.
6. Has a documented weight loss of more than 5% during the 6-month period prior to Randomization (Visit 1/Day 1).

7. Has a history of renal disease defined as an estimated glomerular filtration rate (eGFR) <90 mL/min/1.73 m^2 using the Schwartz Bedside GFR Calculator for Children or present at Screening Visit 1.
8. History of, significant alcohol consumption or inability to reliably quantify alcohol intake, and/or use of illicit drugs.
9. Has clinical and/or historical evidence of cirrhosis, included by not limited to:
    a. Abnormal low hemoglobin as deemed clinically significant by the investigator (with the exception of females with a documented history of a low hemoglobin during menstruation);
    b. White blood cell count < 3,500 cells/mm^3 of blood;
    c. Platelet count <150,000 cells/mm^3 of blood;
    d. Direct bilirubin >0.3 mg/dL;
    e. Total bilirubin >1.3 mg/dL unless the patient has a diagnosis of Gilbert disease in which case direct bilirubin and reticulocyte count do not exceed the upper limit of normal (ULN) and haemoglobin is greater than the lower limit ofnormal;
    f. Serum albumin <3.5 g/dL;
    g. International normalized ratio (INR) >1.4.
10. Has evidence of chronic liver disease other than NASH, defined by any one of the following:
    a. Biopsy consistent with histological evidence of autoimmune hepatitis;
    b. Serum hepatitis A antibody (anti-HAV IgM) positive;
    c. Serum hepatitis B surface antigen (HBsAg) positive;
    d. Serum hepatitis C antibody (anti-HCV) positive;
    e. Serum hepatitis E antibody (anti-HEV) positive;
    f. History of or current positive Anti-Mitochondrial Antibody (AMA)Test;
    g. Known or current Iron/total iron binding capacity (TIBC) ratio (transferrin saturation) > 45% with histological evidence of iron overload;
    h. Known or current Alpha-1-antitrypsin (A1AT) phenotype/genotype ZZ or SZ;
    i. Diagnosis of Wilson's disease.
11. Has a creatine phosphokinase (CPK) greater than the upper limit of normal (ULN) at Screening Visit 1. This test may be repeated , if necessary, to confirm eligibility.
12. Has AST and/or ALT >8 x ULN.
13. Has used any prohibited medication(s) within the specified timeframe (Refer to Appendix III, non-permitted medications):
    a. Within 12 months prior to Screening Visit 1 up to Randomization (Visit 1/Day 1)
        i. Chronic use (defined as treatment longer than 3 consecutive months) of medications known to cause hepatic steatosis or steatohepatitis (including but not limited to systemic chronic glucocorticoids, tetracycline, valproic acid, salicylates, tamoxifen, methotrexate).
    b. Within 12 weeks prior to Screening Visit 1 up to Randomization (Visit 1/Day 1)
        i. Use of Thiazolidinediones (glitazones [pioglitazone & rosiglitazone]).
    c. Within 8 weeks prior to Screening Visit 1 up to Randomization (Visit 1/Day 1)

i. Fibrates medications. Patients taking statins or ezetimibe prior to Screening Visit 1 may participate if the dose has been stable for 3 months prior to Screening Visit 1 and no dose adjustments are anticipated.

14. Is currently taking drugs that could interfere with study medication absorption, distribution, metabolism or excretion or could lead to induction or inhibition of microsomal enzymes, e.g., indomethacin.
15. Is pregnant, lactating or is planning to become pregnant during the study.
16. Is participating in any other study and have received any other investigational drug or device within 30 days prior to Screening or are taking part in a non-medication study which, in the opinion of the Investigator, would interfere with study compliance or outcome assessments.
17. Has symptoms of clinical depression.
18. Has other concurrent medical (e.g., immunological, neoplastic, endocrine, hematological, gastrointestinal or neurological) or psychiatric condition, which, in the opinion of the Investigator, would place the patient at increased risk, preclude obtaining voluntary consent/assent or compliance with required study procedures, or would confound the objectives of study.
19. Has known allergy to the study drug or any of its components.

Primary Endpoint

- Plasma concentrations of elafibranor and its active metabolite GFT1007.

Secondary Endpoints

Pharmacodynamic

- Change from baseline in serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), and alkaline phosphatase (ALP) and other liver markers;
- Change from baseline in glucose homeostasis makers (Homeostatic Model Assessment of Insulin Resistance [HOMA-IR] and fasting insulin), as a continuous measure;
- Change from baseline in serum lipid parameters;
- Change from baseline in body weight and BMI z-score;
- Change from baseline in waist circumference;
- Change from baseline in inflammatory markers;
- Change from baseline in pediatric quality of life (PedsQL™) score.

Safety

- Incidence and severity of treatment emergent adverse events (TEAEs) and their relationship to study drug;
- Incidence of clinically meaningful changes from baseline in safety laboratory parameters, physical examination, electrocardiogram (ECG) and vital signs.

Exploratory Endpoint

- [redacted]

Study Duration (planned)*:* estimated 20 months (First patient first visit [FPFV] to Last patient last visit [LPLV])

- Regulatory/Ethics Committee submission: January 2019
- Initiation visits: March 2019 - April 2019
- FPFV: March 2019
- LPLV: November 2020

Data Safety Monitoring Board (DSMB)

A DSMB will be established to monitor the progress of the study and to perform safety data reviews as designated in the DSMB Charter, in order to protect patient welfare. The DSMB charter will define the role, responsibilities, rules and tasks, schedule, and format of meetings and data review and reporting requirements.

The DSMB considers study-specific data as well as relevant background knowledge about the disease, test agent, or patient population under study. The primary responsibilities of the DSMB are to 1) review and evaluate the accumulated study data for participant safety, study conduct and progress, and 2) make recommendations concerning the continuation (i.e. proceeding with enrollment of patients in cohort 2), modification, or termination of the trial. All DSMB discussions, decisions, and recommendations will be communicated promptly to the sponsor as described in the DSMB Charter.

The DSMB will consist of two independent clinicians with relevant expertise in related NAFLD/NASH pediatric clinical trials and 1 statistician with expertise in clinical trial and interim data analysis.

At a minimum, safety data will be summarized by the statistician after every 5th patient completes visit 4 or available data at the end of each quarter (at approximately 3-month intervals), whichever comes first throughout the study. The DSMB will also review safety and PK data once 80% of the patients in Cohort 1 have completed through Visit 4. Enrollment in Cohort 2 will commence as recommended by the DSMB.

Statistical Considerations

Sample Size

The primary objective of this study is to characterize individual PK parameters in children and adolescents 8 to 17 years of age (inclusive), by collecting rich PK samples to support non-compartmental analysis (NCA). Inter-patient variability of PK parameters in adults was low to moderate (coefficient of variation [CV]% ranged from 23.3% to 68.3%). Assuming a similar degree of variability in pediatric population, a sample size of 20 patients is set to target a 95% CI [confidence interval] within 60% and 140% of the geometric mean estimates of clearance and volume of distribution for elafibranor with at least 80% power (Wang *et al.*, 2012). Additionally, 20 patients should be sufficient to evaluate the safety and tolerability and explore the responsiveness (efficacy) of once daily oral dosing of 80 mg and 120 mg of elafibranor for up to 12 weeks.

Analysis Populations

Three populations will be used for analysis: safety, PK and intent-to-treat. The definition of these populations follows:

- Safety Population: All patients who received at least one dose of study drug and have at least one post-baseline safety assessment.
- Pharmacokinetic Population: All patients who received at least one dose of study drug, do not have protocol deviations or adverse events which may significantly affect PK, and have at least one post-dose PK sample.
- Intent-to-Treat (ITT) Population: All randomised patients who received at least one dose of study drug.

PK and safety data will be analysed based respectively on the PK population and the safety population. Efficacy data will be analysed based on the ITT population.

Primary and Secondary Analysis

Pharmacokinetics

Individual plasma concentrations for elafibranor and its active metabolite GFT1007, will be summarized descriptively (i.e., number of observations, arithmetic mean, standard deviation (SD), % coefficient of variation (CV%), median, minimum and maximum, geometric mean, and % coefficient of variation of the geometric mean (CV% Geometric Mean) by planned time points for each dose group. Individual plasma concentration-time profiles of elafibranor will be plotted on both linear and semi-logarithmic scales. Mean values over time by dose plots will also be presented graphically.

Pharmacokinetic parameters of elafibranor and GFT1007 will be estimated using noncompartmental analysis methods in Phoenix WinNonlin 8.0 or higher, using actual elapsed time from dosing. Plasma concentrations equal to or greater than the qualified lower limit of the assay (LOQ) will be used in the pharmacokinetic analysis. The following calculated PK parameters will include, but not limited to:

- Maximum concentration (C_{max});
- Time to maximum concentration (T_{max});
- Area under the plasma concentration time curve over 24 hours ($AUC_{[0-24]}$);
- Trough concentrations in plasma (C_{trough}).

The analysis plan will be further detailed in the PK Statistical Analysis Plan (PK-SAP).

Safety

- Safety evaluations will consist of adverse events (AEs), vital signs, ECG, and laboratory measurements (hematology, coagulation, biochemistry, and urinalysis) and will be summarized by dose group and overall. Full details will be specified in the SAP.

Efficacy

- Efficacy evaluations will be summarized by dose group and by time point using descriptive statistics and will be based on the change from baseline. Full details will be specified in the SAP.

Exploratory Analysis

- CCI [redacted]

GENERAL STUDY ASSESSMENT SCHEDULE

Visit	Screening Period		Treatment Period						Follow-up Period
	SV1	SV2	V1	V2	V3	V4	V5	V6/End of Treatment[1]	V7/End of Study[7]
Week	-4 to -1	-1 week	0	2	4	4	8	12	16
Visit Day with Permitted Margin	-28 to -7	-5 (±2 days)	1	15 (±2 days)	29 (±2 days)	Day 30	57 (±2 days)	85 (±2 days)	113 (±2 days)
Obtain informed consent / assent	x								
Medical history / demographics	x								
Check inclusion / exclusion criteria	x		x						
Lifestyle modifications (diet and exercise recommendations)	●	—	—	—	—	—	—	—	●
Physical examination	x		x	x	x		x	x	x
Vital signs, height and weight measurement (calculation of BMI z-score)	x		x	x	x		x	x	x
Waist circumference	x		x	x	x		x	x	x
12-Lead electrocardiogram			x					x	
Pediatric Quality of Life (PedsQL™)			x					x	
Lab evaluation (see table "study biological assessment schedule")	x		x	x	x		x	x	x
PK blood sampling			x[2]		x[2]	x[2]		x[2]	
Phone call to the patient		x							
Randomization			x						
Review prior/concomitant medication	x		x	x	x		x	x	x
Adverse events	●	—	—	—	—	—	—	—	●
Study drug dispensing			x		x		x		
Study drug dosing			●	—	—	—	●		
Compliance check (pill count and dosing diary)				x	x		x	x	

Daily[3]

BIOLOGICAL ASSESSMENT SCHEDULE

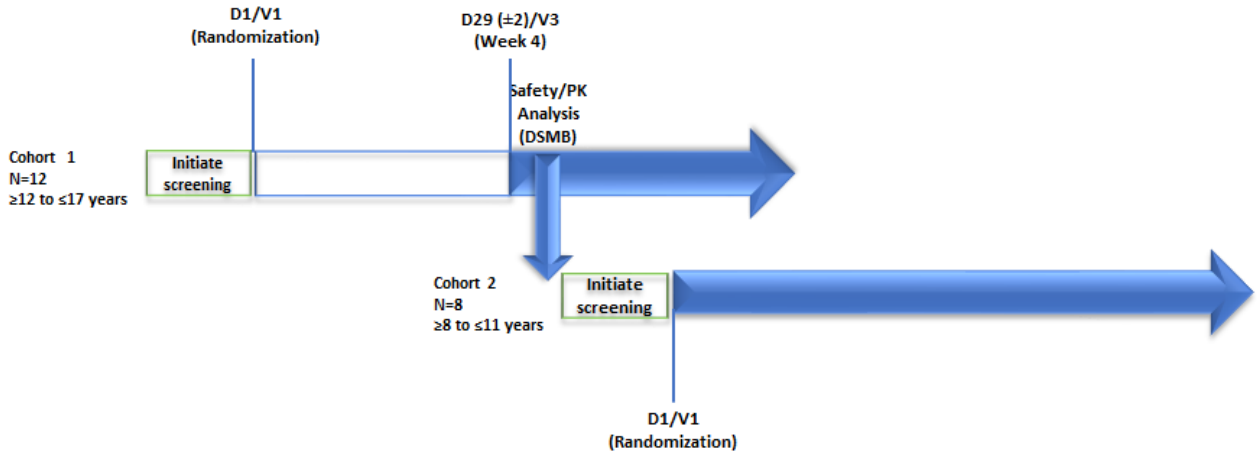
Visit	Screening period	Treatment Period						Follow-up period
	SV1	V1	V2	V3	V4	V5	V6/EOT1	V7/EOS[7]
Week	(-4 to -1)	0	2	4	4	8	12	16
Visit Day with Permitted Margin	-28 to -7	1	15 ± 2 days	29 ± 2 days	30	57 ± 2 days	85 ±2 days	113 ± 2 days
Labs – hematology and coagulation parameters hemoglobin, hematocrit, RBC, WBC, differential count, platelet count, reticulocytes count, prothrombin time (PT) and international normalized ratio (INR)	x	x	x	x		x	x	x
Labs- urine pregnancy testing4	x	x	x	x		x	x	x
Labs – serology HIV, HAV, HBs, HCV and HEV serology	x							
Labs – other parameters for eligibility assessment [5] Antimitochondrial Antibody (AMA), Alpha-1-Antitrypsin Phenotype, Ceruloplasmin, Ferritin, Transferrin Saturation (Serum Iron, Total Iron Binding Capacity)	x[5]							
Labs – biochemistry								
creatinine, creatinine clearance (eGFR), total protein, albumin, electrolytes (sodium, potassium, chloride, calcium), uric acid, urea, CPK, AST, ALT, GGT, alkaline phosphatase, total and conjugated bilirubin, hsCRP, fasting plasma glucose, fasting insulin, HOMA-IR, fructosamine, C-peptide, FFA, HbA1c, TSH, Cystatin C, eGFR from Cystatin C	x	x	x	x		x	x	x
Labs – lipids								
Total Cholesterol, Non HDL-C, HDL-C, TG, calculated VLDL-C, ApoAI, ApoB, LDL-C	x	x	x	x		x	x	x
Inflammatory markers fibrinogen, haptoglobin, TNF-α, IL-6, PAI-1		x		x		x	x	x
Liver markers: CK18 (M65 & M30), adiponectin, ferritin, FGF19 & FGF21, α2 macroglobulin, hyaluronic acid, PIIINP, TIMP-1		x		x		x	x	x

Visit	Screening period	Treatment Period						Follow-up period
	SV1	V1	V2	V3	V4	V5	V6/EOT1	V7/EOS[7]
Week	(-4 to -1)	0	2	4	4	8	12	16
Visit Day with Permitted Margin	-28 to -7	1	15 ± 2 days	29 ± 2 days	30	57 ± 2 days	85 ±2 days	113 ± 2 days
Urinalysis α1 microglobulin, β-NAG, N-Gal, albumin, creatinine, microscopic analysis 6		x		x		x	x	x
Labs – Urinalysis (dipstick) Specific gravity, pH, protein, glucose, ketones, bilirubin, urobilinogen, blood, nitrite, leukocytes		x		x		x	x	x
Labs – Additional samples	x	x					x	
Blood Volume Collected Each Visit	30.3 mL	33 mL	17.3 mL	37.5 mL	1 mL	29.5 mL	32 mL	29.5 mL
Total Volume of Blood Collected Over the Study Period: 210.1 mL								

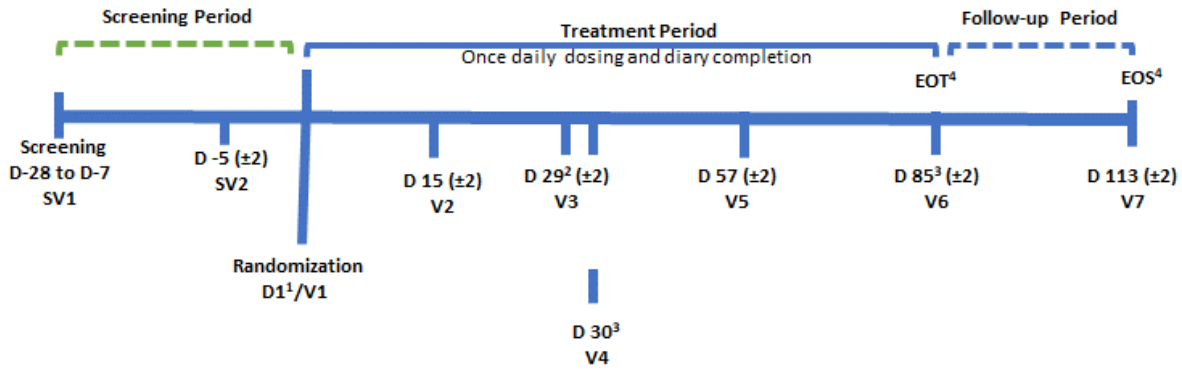
1: If a patient prematurely discontinues, EOT visit procedures must be performed and patient will be encouraged to return for EOS one month later.
2: PK sample collected on Day 1 To (prior to first dose), Day 29, T0 (trough), 0.5 hour (±2 minutes), 1 hour (±2 minutes), 1.5 hour (±2 minutes), 2 hours (±5 minutes), 4 hours (±5 minutes), 6 hours (±10 minutes), and 8 hours (±10 minutes) post dose, Day 30, 24 hours (±10 minutes) after the dose administered the previous day, and Day 85 24 hours (±10 minutes) after the dose administered the previous day.
3: From V1 to V5 the study dosing occurs at site during the visit.
4: Females of childbearing potential (FOCBP) only.
5: Parameters to be analyzed at SV1 only if not screened in the past for these tests (with available results in source documentation).
6: Microscopic analysis is performed centrally in case urinalysis dipstick is abnormal.
7 : If A safety lab parameter is abnormal at visit 7 and is at least 10% higher than the highest reported values obtained between SV1 and V1, an additional visit should be scheduled one month later to repeat those affected parameters.

Figure 1: Study Schematic

A: Enrollment



B: Visit Schedule



Abbreviation: D = day; EOS = end of study; EOT = end of treatment; V = visit
[1] PK sample prior to first dose.
[2] Collection of PK samples: T0 (trough), 0.5 hour (±2 minutes), 1 hour (±2 minutes), 1.5 hour (±2 minutes), 2 hours (±5 minutes), 4 hours (±5 minutes), 6 hours (±10 minutes), and 8 hours (±10 minutes) post dose.
[3] PK sample 24 hour (±10 minutes) after the dose administered the previous day.
[4] Patients that prematurely discontinue study drug, will complete V6 and will be encouraged to complete V7.

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1. INTRODUCTION

1.1. Background

Elafibranor (GFT505), is an orally administered, liver-targeted drug candidate, being developed by Genfit for the treatment of non-alcoholic steatohepatitis (NASH) with fibrosis in adults, and for the treatment of primary biliary cholangitis (PBC). Elafibranor is currently in Phase 3 of development for NASH with fibrosis in an adult population, under CCI [redacted], originally filed in June 2012, and in Phase 2a for PBC under CCI [redacted], filed in September 2016. Phase 1 and 2 clinical studies with elafibranor have been conducted in Europe and the United States (US) and a multi-national Phase 3 registration study is ongoing under IND 115028. A multi-national Phase 2a study is ongoing in PBC under CCI [redacted].

1.2. Mechanism of Action

Elafibranor is a dual peroxisome proliferator-activated receptor (PPAR)α,δ agonist, with a 5-fold selectivity for activation of PPARα over PPARδ. GFT1007 is the main metabolite of elafibranor and shows similar activation of PPARα,δ (Ratziu et al., 2016). Elafibranor improves insulin sensitivity, glucose homeostasis, and lipid metabolism and reduces inflammation.

1.3. Pediatric Non-alcoholic Steatohepatitis

1.3.1. Overview

Pediatric non-alcoholic fatty liver disease (NAFLD) is defined as the full spectrum of disease chronic hepatic steatosis in children (18 years or younger), which is not secondary to genetic/metabolic disorders, infections, use of steatogenic medications, alcohol consumption, or malnutrition (Vos *et al.*, 2017). In most children, NAFLD is associated with insulin resistance, central or generalized obesity, and dyslipidemia characterized by high triglyceride and low high density lipoprotein (HDL) cholesterol levels (Vos *et al.*, 2017). NAFLD is the most common cause of chronic liver disease in children in the United States (US) (Schwimmer *et al.*, 2006).

Based on histology, NAFLD can be divided into nonalcoholic fatty liver (NAFL), which denotes bland steatosis, and nonalcoholic steatohepatitis (NASH), which is marked by steatosis and lobular inflammation and hepatocellular injury (Vos *et al.*, 2017). NASH is a progressive form of liver disease that may lead to advanced fibrosis, cirrhosis, and hepatocellular carcinoma in a subset of affected individuals (Loomba *et al.*, 2009). Children with NASH are at the greatest risk for the most severe outcomes. However, not all children with NAFLD will develop NASH (Pardee *et al.*, 2009).

NAFLD may be suspected based on noninvasive tests, although none of these distinguish between children who have NASH versus children who have NAFL but not NASH (*i.e.*, milder forms of NAFLD). Liver biopsy is required for the definitive diagnosis of NAFLD and the determination of the presence of NASH (Pardee *et al.*, 2009). Pediatric NASH has frequently been observed to show different patterns of inflammation and fibrosis than that seen in adults, with predominantly portal histological changes (Schwimmer *et al.*, 2005; Rashid and Roberts, 2000; Schwimmer *et al.*, 2003).

The prevalence of NAFLD in the general population is estimated at 30% (McPherson *et al.*, 2015). However, the prevalence of pediatric NAFLD is still not well defined (Della Corte *et al.*, 2012).

1.3.2. Natural History

NAFLD in children is distinct from NAFLD in adults in pathophysiology, clinical course, and treatment response (Schwimmer *et al.*, 2005). These differences may be due in part to the occurrence of hepatic metabolic derangements typical of NAFLD during periods of active growth (infancy, mid-childhood and puberty) (Roberts, 2007). Moreover, hormonal changes during puberty may potentiate fat accumulation in the liver (Loomba *et al.*, 2009) (Goyal and Schwimmer 2016) (Quiros-Tejeira *et al.*, 2007) (Modi *et al.*, 2011).

Among the adult population, it is believed that simple hepatic steatosis is generally non-progressive, while NASH may lead to progressive liver disease (Fazel *et al.*, 2016). In the adult population, the progression of NASH can take years to manifest. In this context, the presence of type 2 diabetes and the severity of histologic features such as ballooning degeneration of hepatocytes can be important predictors of fibrosis progression, but only the stage of fibrosis predicts liver mortality (Liou and Kowdley, 2006). Similarly, evidence suggests that that among the pediatric population, insulin resistance and obesity are important predictors of progression (Schwimmer *et al.*, 2003). A longitudinal follow-up study on former pediatric NAFLD patients indicated a high rate of type 2 diabetes (30%) and the persistence of obesity into young adulthood (Cioffi *et al.*, 2017). Factors that account for differences between children with NASH versus children with milder forms of NAFLD are unclear (Pardee *et al.*, 2009).

At diagnosis, 10–25% of children can have advanced fibrosis. In the most severe cases, children can progress within a few years to cirrhosis and end-stage liver disease. Quality longitudinal data of the natural history of pediatric NAFLD are limited. However, available data suggest that children with NAFLD are at risk for higher mortality rates as young adults (Goyal and Schwimmer, 2016).

The natural history of pediatric NAFLD in the setting of lifestyle counselling was represented by the placebo arm of the treatment of non-alcoholic fatty liver disease in children (TONIC) trial, a 2-year randomized control trial designed to compare vitamin E, metformin, and placebo with liver biopsies at baseline and at 2-year follow-up. All 3 arms received nutrition and physical activity (lifestyle) advice. In the placebo cohort, 28% had resolution of NASH, 40% improved fibrosis, 40% improved steatosis, and 43% improved lobular inflammation. Progression of disease was seen in 25% (Lavine *et al.*, 2011).

Although limited, the pediatric data on the natural history of pediatric NAFLD support some conclusions. Fifteen percent of children with NAFLD have stage 3 fibrosis or higher at diagnosis (Schwimmer *et al.*, 2014) and disease in children appears to be more severe compared with adults (Holterman *et al.*, 2013). Given that pediatric disease is by definition early onset disease, it may represent an aggressive phenotype of the disease. Reports show that a few children have rapid progression to clinical events from NAFLD (death, transplant, diabetes, CVD). Because such clinical events from pediatric NAFLD typically do not occur under the age of 21 years, studies determining clinical outcomes from pediatric NAFLD will require long-term follow-up into adulthood (Vos *et al.*, 2017).

1.3.3. Diagnosis

The diagnosis of NASH begins with the clinical suspicion of liver disease in a child. NAFLD may be suspected on the basis of an elevated serum alanine aminotransferase (ALT), hepatomegaly, or an abnormal imaging study consistent with fatty liver. In children, NAFLD is typically diagnosed between the ages of 10–13 years but the actual onset of disease for most children is not known (Goyal and Schwimmer, 2016).

Interpretation of liver histology is required to confirm a diagnosis of NAFLD, and to identify the presence and severity of NASH (Pardee *et al.*, 2009). Not all children with NAFLD will develop NASH (Pardee *et al.*, 2009).

Pediatric NASH is a histological diagnosis divided into two types:

- Type 1: Liver biopsies consistent with adult histology. Defined as presence of steatosis with ballooning degeneration and/or perisinusoidal fibrosis, without portal involvement.
- Type 2: Liver biopsies are unique in appearance. Defined as the presence of steatosis with portal inflammation and/or fibrosis, in the absence of ballooning degeneration or perisinusoidal involvement.

Though the biological mechanisms behind the subtypes are currently unknown, these findings highlight a potentially important distinction between adult and pediatric NASH (Pardee *et al.*, 2009). Identification of fibrosis in children with NASH and NAFLD is important because these phenotypes are expected to be more likely to progress to cirrhosis (Loomba and Chalasani, 2015). Overt signs and symptoms of advanced fibrosis or cirrhosis are, however, uncommon in children with NAFLD and NASH (Vos *et al.*, 2017).

1.3.4. Prevalence

Prevalence of NAFLD varies by race/ethnicity. US studies have revealed a 4-fold increased risk of hepatic steatosis in Hispanic, compared with non-Hispanic adolescents (11–22 years old) (Rehm *et al.*, 2014). White and Asian children also have high prevalence, compared to African American children (Schwimmer *et al.*, 2006). The prevalence also differs by sex, with most studies showing higher percentages in male compared to females (Pardee *et al.*, 2009). However, males and females appear to be equally likely to have NASH (Goyal and Schwimmer, 2016). Prevalence is higher in obese children compared with normal weight, although not all children with NAFLD are obese (Schwimmer *et al.*, 2006).

Anderson *et al* (Anderson *et al.*, 2015), conducted a systematic review and meta-analysis of all studies reporting a prevalence of NAFLD based on any diagnostic method (i.e. biopsy, ultrasound, magnetic resonance imaging or other scans or liver enzymes) in participants 1–19 years old, regardless of whether assessing NAFLD prevalence was the main aim of the study. The commonest serum biomarkers used to assess NAFLD prevalence in research settings and to identify patients who may benefit from further investigation in clinical settings are alanine aminotransferase (ALT) and aspartate aminotransferase (AST) (Golberg, 1980 [reported in Anderson *et al.*, 2015]). Both liver enzymes have been reported to correlate with the degree of liver fat infiltration, inflammation (Anderson *et al.*, 2015). Prevalence of NAFLD ranges from 9 to 37% (Jou, 2008; Hesham, 2009 [reported in Anderson *et al.*, 2015]). In one study of NAFLD in children, about 23% had NASH (Schwimmer *et al.*, 2006).

1.4. Summary of Studies with Elafibranor

1.4.1. Nonclinical Experience

No safety issues were identified when assessing the potential effects of elafibranor on the cardiovascular, respiratory, and central nervous systems. 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 all species, maximal plasma concentrations and exposure for both elafibranor and GFT1007 increase with the dose after single or repeated administrations. Elafibranor and its metabolites are rapidly cleared from the plasma and are mainly excreted by the fecal route, with urinary excretion as a secondary route of elimination. 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. Tissue distribution studies in rodents and monkeys support the liver targeting of elafibranor and/or its metabolites.

The toxicology program performed according to ICH guidelines demonstrates that elafibranor has no genotoxic or mutagenicity potential. According to acute toxicity study results, it can be concluded that elafibranor is 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. 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.

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 humans (Cattley, 1998). Overall, these studies did not reveal any other safety issues up to the highest doses tested. Notably, elafibranor did not show any of the known PPARγ-related concerns such as excess weight gain, hemodilution, edema, cardiomegaly, adiponectin induction, or urinary bladder carcinoma.

The phototoxic potential of elafibranor has been assessed by the in vitro 3T3 NRU phototoxicity test and the ultraviolet (UV)-Local Lymph Node Assay (LLNA) test in mice. Elafibranor, 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 NOEL was set at 400

mg/kg/day based on isolated findings at the highest dose, it is considered that data are more in favour of an absence of phototoxic effect, given the tissue distribution of elafibranor, and absence of phototoxicity signal in all clinical studies.

To support dosing in children, a juvenile toxicity study has recently been performed in rats, with administration of elafibranor from post-natal day (PND) 21 to PND 63 (6 weeks). An assessment of delayed onset toxicity and/or reversibility of toxicity was made following a 4 week recovery period. Overall, changes observed during the study were either minor and monitorable (and at least partially reversible), or recognized adaptive changes associated with the PPARα agonist class of compound in the rat. Therefore, the no observed adverse effect level (NOAEL) for male and female juvenile rats was considered to be 100 mg/kg/day elafibranor.

1.4.2. Clinical Experience

Overall, a total of 2511 subjects have been randomized in the elafibranor clinical program, of which it is estimated that 1704 were exposed to elafibranor (based upon actual exposure data from completed clinical trials and the enrollment/randomization schemes for ongoing trials). These studies have been conducted in adult patients aged 18 to 75 years of age.

Overall, 549 healthy subjects, 60 obese but otherwise healthy subjects, 37 patients with mixed hyperlipidaemia (type IIb Frederickson), 94 patients with atherogenic dyslipidaemia and abdominal obesity, 47 patients with impaired glucose tolerance and abdominal obesity, 109 diabetes mellitus type 2 patients, 22 patients with insulin resistance and abdominal obesity, 1548 NASH patients and 45 PBC patients were randomized and treated in clinical trials to date. Of these, 406 healthy subjects, 45 obese but otherwise healthy subjects, 24 patients with mixed hyperlipidaemia, 63 patients with atherogenic dyslipidaemia and abdominal obesity, 23 patients with impaired glucose tolerance and abdominal obesity, 59 diabetes mellitus type II patients, 22 patients with insulin resistance and abdominal obesity, and an estimated 1032 NASH patients and 30 PBC patients received elafibranor, based upon actual exposure data from completed clinical trials and the enrollment/randomization schemes for ongoing trials.

Clinical data have confirmed the potential beneficial effect of elafibranor in subjects with metabolic disorders and NASH.

Phase 2 studies in subjects with cardiometabolic disorders and NASH have demonstrated consistent reductions in ALP compared to placebo. The reduction in ALP was associated with relevant reductions in markers of liver injury such as GGT and ALT and in inflammatory markers. These data are encouraging to consider elafibranor as a potential drug candidate to treat PBC.

In addition, the Phase 2b trial in adult NASH patients 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 low density lipoprotein-cholesterol (LDL-C), increasing high density lipoprotein-cholesterol (HDL-C), 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.

A Phase 3 study in subjects with NASH and fibrosis is ongoing with up to 2224 patients to be enrolled and, to date, more than half of the subjects have been randomized. In this study, subjects are receiving 120 mg/day elafibranor or placebo for up to 72 weeks during the first treatment period, followed by a long-term treatment period 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 of portal hypertension or cirrhosis-related events.

These studies have highlighted the good safety profile of elafibranor and no major safety concerns have been raised. Based on the cumulative experience gathered to date, gastrointestinal 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 2 studies to date and is a known PPARα agonist effect. Elevation of transaminases should also be monitored as well as drug-induced liver injury. In the absence of 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. A DSMB has been reviewing the safety data of the ongoing phase 3 study every 6 months in an unblinded manner and has not raised any safety signal.

In conclusion, the safety data and the current knowledge on elafibranor confirm the favourable balance between anticipated efficacy/benefits and risks.

For additional detailed information see current version of Investigator's Brochure.

1.5. Rationale for Elafibranor in Pediatric Population

1.5.1. Rationale for Elafibranor in Pediatric NASH

The goal of treatment of pediatric NAFLD and NASH is to stop and reverse liver injury (Nobili *et al.*, 2014). Lifestyle modification is the current first-line therapy for pediatric NAFLD and NASH, even though it is difficult to obtain and to maintain (Della Corte *et al.*, 2014). There is no approved pharmacological therapy for NAFLD and NASH in children or adults (Loomba *et al.*, 2009).

As described above, pre-clinical studies have shown that elafibranor reverses histological NASH and liver fibrosis in multiple pre-clinical models of NAFLD/NASH, reducing hepatic inflammation and normalizing liver enzymes. In addition, elafibranor improves dyslipidemia in numerous preclinical models, and has insulin-sensitizing and glucose-lowering properties in experimental models of type 2 diabetes.

Possible PPAR-related side-effects have been considered in order to assess the benefit-risk of the use of elafibranor in pediatric populations. Most of the PPAR-related safety concerns described in humans are associated with the PPAR γ isoform, notably those reported with PPAR γ agonists on cardiovascular risks.

They are therefore not relevant to elafibranor, which shows no evidence of PPAR γ -associated activity in vivo. In particular, there is no evidence of cardiomegaly or increased risk of cardiac insufficiency that have been associated with PPAR γ agonists (Nesto *et al.*, 2003).

PPARα associated liver and related tumors observed in two-year rodent carcinogenicity studies with elafibranor are rodent specific and are not considered relevant to humans.

The proposed 3-month study in the 8-17 year old pediatric population will allow to obtain the PK/PD profile and the safety data under close monitoring in highly-recognized academic settings.

Overall, the non-clinical data, along with clinical studies to date, support the use of elafibranor for the treatment of fatty liver diseases (NAFLD/NASH) and hepatic fibrosis, with associated benefit on atherogenic dyslipidemia (high triglycerides, low HDL-cholesterol), glucose homeostasis and insulin resistance, and inflammatory status.

There is currently no evidence to suggest that the therapeutic activity of elafibranor may be different in children compared to the adult. Taking into account, the prevalence of NAFLD in children, and the beneficial effects of elafibranor on liver damage and on the various components of the metabolic syndrome, we therefore propose NAFLD as a treatment indication for elafibranor in children.

1.5.2. Rationale for the Study Population

Patients enrolled in this study are children and adolescents (8 to 17 years old, inclusive) will be representative of the pediatric population with NASH that will include patients without fibrosis and some with significant (stage 2 or 3) fibrosis. In addition, they have metabolic abnormalities, suffer from overweight (BMI z-score > 85th percentile) and insulin resistance (HOMA-IR ≥ 5). These abnormalities

represent the basis for the development of their liver disease, with insulin resistance being the central element of progression of NAFLD.

As elafibranor has consistently demonstrated clear efficacy on metabolic parameters, insulin resistance and inflammation in the phase 2a program and in the phase 2b, it is expected that the patients will all have a clinical benefit with elafibranor treatment, which addresses the metabolic abnormalities present at the early stage of NAFLD.

The safety will be closely monitored in high level academic sites.

1.5.3. Justification of the Selected Dose

The results obtained in the phase 2 program showed that both doses of elafibranor 80mg and 120mg beneficially affect the metabolic parameters such as plasma lipids, glucose homeostasis, and insulin resistance in the adult population.

In all studies currently performed (including the ongoing phase 3 study monitored by a DSMB), a good safety profile of elafibranor has been demonstrated. Due to the overweight/obese profile of the targeted population in this first pediatric study (inclusion criteria related to minimum BMI z-score), dose intended to be used on this study are similar to the ones used in phase 2b and phase 3 studies.

Therefore, given the good safety profile and the efficacy of elafibranor 80 and 120mg, both doses will be tested in this pediatric study.

The PK data obtained in this study will be used to confirm the dose to be used in future studies in children and adolescents (8 to 17 years old).

1.5.4. Rationale for the Study

The present short-term study will provide important preliminary information related to pharmacokinetics, safety, tolerability, and efficacy (including metabolic function) in this pediatric population. The study results will inform the development of the pediatric formulation and optimize the design of future studies.

2. TRIAL OBJECTIVES

2.1. Primary Objective

To assess the pharmacokinetic profile of elafibranor and its active metabolite GFT1007, following once daily oral administration of two dose levels of elafibranor (80 and 120 mg) to children and adolescents, 8 to 17 years of age (inclusive).

2.2. Secondary Objectives

- To assess changes in serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), and alkaline phosphatase (ALP) and other liver markers;
- To assess changes in markers of glucose homeostasis (homeostatic model assessment for insulin resistance (HOMA-IR) and fasting insulin);
- To assess changes in serum lipid parameters;
- To assess changes in body weight and BMI z-score;
- To assess changes in waist circumference;
- To assess changes in inflammatory markers;
- To assess the change in the pediatric quality of life (PedsQL™) score as completed by the child/adolescent and the parent/legal guardian.

2.3. Safety Secondary Objective

To assess the safety and tolerability profile of two dose levels of elafibranor (80 mg and 120 mg) in children and adolescents, 8 through 17 years of age.

2.4. Exploratory Objective

CCI [redacted]

3. TRIAL DESIGN

This study is an open-label, randomized, multicenter, sequential cohort study that will assess the pharmacokinetics (PK), safety, and pharmacodynamics (PD) and explore the relationship between PK and PD response following 12 weeks of once daily oral administration of elafibranor at doses of 80 mg and 120 mg in children and adolescents, 8 to 17 years of age (inclusive), with histologically confirmed (historical biopsy) nonalcoholic steatohepatitis (NASH). The target population will include patients with NASH with and without fibrosis. Of the 20 patients that will be enrolled and dosed with elafibranor, at least 4 patients ≥12 to ≤17 years of age and at least 2 patients ≥8 to ≤11 years of age will have significant fibrosis [i.e., fibrosis stage 2 or 3]).

Two patient cohorts will be dosed sequentially. Cohort 1 will consist of approximately 12 patients who are ≥12 to ≤17 years of age and will be enrolled first. Once 10 (80%) patients in cohort 1 have been evaluated for PK and safety through Visit 4 by the Data Safety Monitoring Board (DSMB), and if agreed upon by the DSMB, enrollment will be open to patients ≥8 to ≤11 years of age. Cohort 2 will consist of approximately 8 patients who are ≥8 to ≤11 years of age.

Potential patients will be screened within 28 days (-28 [Week -4] to -7 [Week -1]) prior to Day 1. Day 1 will include randomization and dosing with study drug. After signing the ICF (parent/legal guardian) and assent (patient) documents, patients will undergo screening procedures to confirm study eligibility. The patient (and parent/guardian) will be given counselling regarding a diet and exercise regimen to be maintained starting from the Screening visit.

Eligible patients will return to the clinic on Day 1. Baseline evaluations including confirmation of continued study eligibility, physical examination, height/weight and waist circumference, vital signs, 12-lead safety electrocardiogram (ECG), clinical laboratory evaluations (including pre-dose pharmacokinetic (PK) sample, biological assessments and safety assessments), collection of adverse events (AEs) and concomitant medications, baseline Pediatric Quality of Life (PedsQL™) completed by the patient and the parent/legal guardian], and pregnancy test (for females of childbearing potential [FOCBP]), will be obtained prior to study drug administration. Patients will be randomized (1:1) to receive either 80 mg or 120 mg once daily for 12 weeks. The patient (and parent/legal guardian) will again be counselled on dietary and exercise regimen requirements that will be maintained throughout the study period. Patients will be dispensed a 1-month supply of study drug and dosing diary and will be scheduled for their next visit on Day 15 (± 2 days) for safety, PD (biological laboratory assessments) evaluation and compliance check.

The patient will return on Day 29 (± 2 days)/Week 4 for safety, PD (biological laboratory assessments), PK assessments, and compliance check. A pre-dose PK sample will be obtained, and the daily dose of study drug will be given in the clinic. PK samples will be collected at 0.5 hours (±2 minutes), 1-hour (±2 minutes), 1.5 hours (±2 minutes), 2 hours (±5 minutes), 4 hours (±5 minutes), 6 hours (±10 minutes), and 8 hours (±10 minutes) post dose. A 1-month supply of study drug and dosing diary will be dispensed. The patient will return the following day for collection of the 24 hour (±10 minute) post-dose sample (prior to next daily dose). The patients will return to the clinic on Day 57 (± 2 days)/Week 8 and Day 85 (± 2 days)/Week 12 EOT visit, for safety and PD (biological laboratory assessments) evaluations and compliance evaluations. On Day 57, in addition to safety and PD, a 1-month supply of study drug and dosing diary will be dispensed. At the End of Treatment (EOT) visit, Day 85 (± 2 days)/Week 12, quality of life will be assessed, the final PK sample will be collected, and unused study drug and completed dosing diary will be collected. A final safety evaluation will be conducted on EOS visit, Day 113 (± 2 days)/Week 16.

3.1. Study Schedule

Each patient may participate in the study for up to approximately 20 weeks (Screening through final follow-up visit).

- Screening:
  - SV1 Week -4 to Week -1: Day -28 to Day -7
  - SV2 Week -1: Day -5 (±2 days) (telephone contact only)
- Randomization and Treatment: Day 1 to Day 85 (±2 days)
  - V1 Week 0 (Randomization): Day 1
  - V2 Week 2: Day 15 (±2 days)
  - V3 Week 4: Day 29 (±2 days)
  - V4 Week 4: Day 30 (24h PK sample collection)
  - V5 Week 8: Day 57 (±2 days)
  - V6 Week 12 (EOT): Day 85 (±2 days)
- Follow-up: Day 86 to Day 113 (±2 days) (Week 12 to Week 16)
  - V7 Week 16 (EOS): Day 113 (±2 days)

3.2. Randomization

Number of Randomized Patients (planned): A total of 20 patients will be enrolled across the two cohorts.

- Cohort 1: ≥12 to ≤17 years of age. A total of approximately 12 patients will be randomized in this cohort.

- Cohort 2: ≥8 to ≤11 years of age. A total of approximately 8 patients will be randomized in this cohort. Enrollment in this cohort will not start until 80% of the patients in cohort 1 have been evaluated through Visit 4 by the Data Safety Monitoring Board and a recommendation by the DSMB to continue the study has been made.

Patients will be randomized 1:1 to receive either dose (80 or 120 mg).

Considering that at least 4 patients ≥12 to ≤17 years of age and at least 2 patients ≥8 to ≤11 years of age with fibrosis stage 2 or 3 will be enrolled and to achieve balance between dosing groups according to the fibrosis severity, randomization will be stratified within each cohort based upon screening fibrosis severity stage (stratum 1:fibrosis stage 0 to 1 and stratum 2: fibrosis stage 2 to 3).

4. PATIENT SELECTION

4.1. Inclusion Criteria

For a study patient to be evaluated for study participation:

1. Parent(s)/Legal Guardian(s) must provide written Informed Consent (including HIPAA) prior to the conduct of any study related procedures to permit participation of a minor in a clinical research study in accordance with federal and local laws. Additionally, assent from a minor child will be obtained in accordance with federal and local laws as well as in compliance with the recommendations of the approving Institutional Review Board (IRB)/Independent Ethics Committee (IEC).

Study patients will be eligible for inclusion in the study if they meet all the following criteria at Screening and up to the time of Randomization (Visit 1) as applicable:

2. Are male or female between 8 and 17 years of age (inclusive) at the time of Screening Visit 1 (when consent for study participation is given) and at the time of Randomization (Visit 1).

3. Diagnosis of non-alcoholic steatohepatitis (NASH) confirmed by histological evaluation (with or without fibrosis) from a liver biopsy obtained within 24 months prior to Randomization (Visit 1/Day 1).

4. Has adhered to a minimum of 3 months of lifestyle modification to treat NASH, prior to Screening (SV1), and agrees to adhere to lifestyle modifications (diet and exercise) throughout the study period (Screening through final visit [Visit 7/Day 113]).

5. Has an alanine aminotransferase (ALT) level greater than (>) 50 IU/L, at Screening (SV1).

6. Has a Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) ≥ 5, at Screening (SV1).

7. Has a Body Mass Index z-score (BMI z-score) (also referred to as BMI-for-age percentile) greater than or equal to (≥) 85th percentile for age and gender at Screening (SV1).

8. Has a Hemoglobin A1C (HbA1c) less than or equal to (≤) 8.5%. If the patient has Type 2 diabetes and is taking anti-diabetic therapy (e.g., metformin or insulin), treatment must have been started at least 3 months prior to Screening (SV1) and the dose must be stable for at least 3 months prior to Screening (SV1) and should remain stable through Randomization (Visit 1/Day 1).

9. If patient is taking medications or supplements to treat NAFLD/NASH (Vitamin E, ursodeoxycholic acid, PUFAs), the dose must be stable for at least 3 months prior to Screening Visit 1 and should remain stable through Randomization (V1/Day 1) and planned to remain stable through EOS.

10. Sexually active female participants of childbearing potential must agree to utilize a highly effective method of contraception per the Clinical Trial Facilitation Group (CTFG) Guidelines (refer to Appendix IV), from Screening through 30 days after the last dose of study drug (1 month after the end of treatment (EOT), and agree to monthly pregnancy testing during the study up to and including EOS.

11. The Parent(s)/Legal guardian(s) and study patient are willing and able to follow all study-related procedures, including but not limited to daily study drug administration, pharmacokinetic (PK) sampling, be willing and able to return to the study clinic for study visits and be accessible by phone or e-mail for study related communications.

12. Patient agrees not to consume alcohol or use illicit drugs during the study up to and including EOS.

4.2. Exclusion Criteria

A study patient will be excluded from the study if they meet any of the following criteria at Screening (SV1) or prior to Randomization (Visit 1/Day 1):

1. Has history of bariatric surgery or planned surgery during the study period

2. Has known history of heart disease.

3. Has uncontrolled hypertension evidenced by sustained elevation in systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg despite treatment with antihypertensive therapy, prior to Randomization (Visit 1/Day 1).

4. Has a known history of Type 1 diabetes.

5. Has a known history of acquired immunodeficiency syndrome or positive screening for human immunodeficiency virus antibodies at Screening Visit 1.

6. Has a documented weight loss of more than 5% during the 6-month period prior to Randomization (Visit 1/Day 1).

7. Has a history of renal disease defined as an estimated glomerular filtration rate (eGFR) <90 mL/min/1.73 m^2 using the Schwartz Bedside GFR Calculator for Children or present at Screening Visit 1.

8. History of, significant alcohol consumption or inability to reliably quantify alcohol intake, and/or use of illicit drugs.

9. Has clinical and/or historical evidence of cirrhosis, included by not limited to:

    a. Abnormal low hemoglobin as deemed clinically significant by the investigator (with the exception of females with a documented history of a low hemoglobin during menstruation);

    b. White blood cell count < 3,500 cells/mm^3 of blood;

    c. Platelet count <150,000 cells/mm^3 of blood;

    d. Direct bilirubin >0.3 mg/dL;

    e. Total bilirubin >1.3 mg/dL unless the patient has a diagnosis of Gilbert disease in which case direct bilirubin and reticulocyte count do not exceed the upper limit of normal (ULN) and haemoglobin is greater than the lower limit of normal;

    f. Serum albumin <3.5 g/dL;

    g. International normalized ratio (INR) >1.4.

10. Has evidence of chronic liver disease other than NASH, defined by any one of the following:

    a. Biopsy consistent with histological evidence of autoimmune hepatitis;

    b. Serum hepatitis A antibody (anti-HAV IgM) positive;

    c. Serum hepatitis B surface antigen (HBsAg) positive;

    d. Serum hepatitis C antibody (anti-HCV) positive;

    e. Serum hepatitis E antibody (anti-HEV) positive;

    f. History of or current positive Anti-Mitochondrial Antibody (AMA)Test;

    g. Known or current Iron/total iron binding capacity (TIBC) ratio (transferrin saturation) > 45% with histological evidence of iron overload;

    h. Known or current Alpha-1-antitrypsin (A1AT) phenotype/genotype ZZ or SZ;

    i. Diagnosis of Wilson's disease.

11. Has a creatine phosphokinase (CPK) greater than the upper limit of normal (ULN) at Screening Visit 1. This test may be repeated , if necessary, to confirm eligibility.

12. Has AST and/or ALT >8 x ULN.

13. Has used any prohibited medication(s) within the specified timeframe (Refer to Appendix III, non-permitted medications):

    a. Within 12 months prior to Screening Visit 1 up to Randomization (Visit 1/Day 1)

        i. Chronic use (defined as treatment longer than 3 consecutive months) of medications known to cause hepatic steatosis or steatohepatitis (including but not limited to systemic chronic glucocorticoids, tetracycline, valproic acid, salicylates, tamoxifen, methotrexate).

    b. Within 12 Weeks prior to Screening Visit 1 up to Randomization (Visit 1/Day 1)

        i. Use of Thiazolidinediones (glitazones [pioglitazone & rosiglitazone]).

    c. Within 8 Weeks prior to Screening Visit 1 up to Randomization (Visit 1/Day 1)

        i. Fibrates medications. Patients taking statins or ezetimibe prior to Screening Visit 1 may participate if the dose has been stable for 3 months prior to Screening Visit 1 and no dose adjustments are anticipated.

14. Is currently taking drugs that could interfere with study medication absorption, distribution, metabolism or excretion or could lead to induction or inhibition of microsomal enzymes, e.g., indomethacin.

15. Is pregnant, lactating or is planning to become pregnant during the study.

16. Is participating in any other study and have received any other investigational drug or device within 30 days prior to Screening or are taking part in a non-medication study which, in the opinion of the Investigator, would interfere with study compliance or outcome assessments.

17. Has symptoms of clinical depression.

18. Has other concurrent medical (e.g., immunological, neoplastic, endocrine, hematological, gastrointestinal or neurological) or psychiatric condition, which, in the opinion of the Investigator, would place the patient at increased risk, preclude obtaining voluntary consent/assent or compliance with required study procedures, or would confound the objectives of study.

19. Has known allergy to the study drug or any of its components.

5. TRIAL PROCEDURES

The procedures performed at each visit are summarized in Section 5.2 and in the General Study Assessment Schedule and Biological Assessment Schedule. However, a patient may be seen at any time for safety reasons and will be recorded as an unscheduled visit.

5.1. Lifestyle Recommendations and Study Recommendations

5.1.1. Diet and Lifestyle Recommendations

Standard diet and exercise recommendation given by the Investigator during Screening Visit 1 will be given at the beginning of each patient's participation and will be maintained throughout the study.

These recommendations will be based on the latest recommendations from the American Academy of Pediatrics (AAP) (Birch *et al.*, 2006).

5.1.2. Dietary, Fluid and Lifestyle Restrictions

The following restrictions apply to patients in this trial from Screening Visit 1 through the end of the study:

- Patients will be required to fast (no food or drink other than water) for at least 10 hours prior to blood sampling (except for the post-dose PK blood sampling). As such, patients should not consume any breakfast or take study medication in the morning prior to the blood sampling. In case the patient does not fast before a visit, a new appointment will be scheduled to occur within 4 days.
- On each study visit day (with the exception of Visit 4/ Day 30), study treatment will be taken under fasting conditions after the blood sampling.
- During the 48 hours preceding each study visit, patients should not perform strenuous exercise.
- Alcohol should not be consumed during the study (through EOS visit).
- Illicit drugs should not be used during the study (through EOS visit).

5.2. Trial Procedures at Each Visit

The procedures and assessments to be performed at each visit are indicated in the General Study Assessment Schedule, Biological Assessment Schedule, and Figure 1: Study Schematic. When planning study visits, all subsequent visits should be calculated based off of Visit 1 (Day 1). An estimated time for the conduct of each visit is provided as a guide only to the study site personnel and study patient and parent/legal guardian for planning purposes. Note: it will not be considered a departure from the protocol if the visit length is shorter or longer than anticipated.

5.2.1. Screening Visit 1/Week -4 to Week -1 (Day -28 to Day -5 (±2 days))

The screening visit can occur up to 4 weeks prior to randomization but should occur at least 1 week prior to planned randomization to ensure the results of laboratory test are available to verify inclusion/exclusion criteria. Due to the COVID-19 crisis, the screening window (i.e., the time from the signing of consent / screening visit 1 to randomization) can be extended to be up to 8 weeks if no onsite visit is possible earlier.

It is estimated that this visit will take approximately 2 hours to complete the visit.

- Informed Consent Process
  - The parent(s)/legal guardian (s) must provide written informed consent prior to any study procedure being done; and
  - The patient must provide assent to participate in the study.
- Interview
  - Evaluate Inclusion/Exclusion Criteria;
  - Review and record demographic information;
  - Review and record prior medications (those taken within the last 12 months and current medications);
  - Review prior medical and surgical histories;
  - Assess potential alcohol intake by AUDIT questionnaire interview of patient.
- Assessments
  - Measure and record height, weight, waist circumference, and calculate BMI z-score;
  - Obtain and record vital signs;
  - Perform a complete physical examination.
- Sample Collection

- Collect fasting blood samples as indicated on the General Study Assessment Schedule;
- Collect urine sample for urinalysis (UA) and urine pregnancy test (if applicable).

- Instructions
  - Inform Parent/legal guardian and patient that they will be contacted within approximately 1 week regarding study qualification and will be scheduled for Visit 1 (as applicable).
  - Counselling regarding a diet and exercise regimen that should be maintained starting from the screening visit.
- Screen Visit 2 – Phone Contact Week -1
  - Inform Parent/legal guardian and patient of qualification status and schedule for Day 1 (randomization).
  - When Visit 1 is scheduled inform the parent/guardian the patient must present for Visit 1 in a fasted state (nothing to eat or drink (except water) for 10 hours prior to the visit).

5.2.2. Visit 1/Week 0/ Day 1 (Randomization)

It is estimated that this visit will take approximately 2 hours to complete the visit.

- Interview
  - Confirm patient continues to meet Inclusion/Exclusion Criteria;
  - Review of adverse events;
  - Review concomitant medications.
- Assessments
  - Measure and record height, weight, waist circumference, and calculate BMI z-score;
  - Obtain and record vital signs;
  - Obtain 12-lead Electrocardiogram (ECG);
  - Perform a complete physical examination;
  - Patient and parent/legal guardian to self-complete the PedsQL™ questionnaire individually.
- Sample Collection
  - Collect fasting blood samples as indicated on the General Study Assessment Schedule;
  - Collect urine sample for UA and for urine pregnancy testing (as applicable and locally tested).
- Randomization and Dosing
  - Randomize patient to study treatment;
  - Administer the first dose of study drug in the clinic. Dose will be given with a minimum of 50 mL of water and check that study drug is swallowed.
- Instructions
  - Counselling regarding a diet and exercise regimen that should be maintained starting from the screening visit.
  - Review dosing procedure and completion of dosing diary (refer to Appendix II) and dispense 1-month supply of study drug. Patient's should be instructed not to discard used wallet cards, rather, the used wallet cards should be kept and returned with the box to the study site at the next study visit (Visit 2).
  - Remind the parent/legal guardian/patient to present for Visit 2 in a fasted state (nothing to eat or drink (except water) for 10 hours prior to the visit).
  - Remind the patient to not take any dose the day of Visit 2 before presenting to the clinic.

5.2.3. Visit 2/Week 2 (Day 15 ±2 days)

It is estimated that this visit will take approximately 1 hour to complete the visit.

- Interview
  - Review of adverse events;
  - Review concomitant medications.
- Assessments
  - Measure and record height, weight, waist circumference, and calculate BMI z-score;
  - Obtain and record vital signs;
  - Perform a complete physical examination.
- Sample Collection
  - Collect fasting blood samples as indicated on the General Study Assessment Schedule;
  - Collect urine sample for urine pregnancy testing (as applicable and locally tested).
- Compliance Check
  - Pill count;
  - Review diary;
  - Administration of dose in the clinic. Dose will be administered with approximately 50 mL of water and check that study drug is swallowed.
- Instructions
  - Counselling regarding a diet and exercise regimen that should be maintained throughout the study.
  - Review dosing procedure and completion of dosing diary (refer to Appendix II). Re-dispense study drug to the patient.
  - Remind the parent/legal guardian/patient to present for Visit 3 in a fasted state (nothing to eat or drink (except water) for 10 hours prior to the visit).
  - Remind the patient not to take any dose of study medication the day of Visit 3 before presenting to the clinic.

5.2.4. Visit 3/Week 4 (Day 29 ±2 days)

It is estimated that the total visit time will be approximately 8-1/2 hours. Patients will remain in the clinic for the collection of PK samples through hour 4. Patients may leave the clinic and return for the 6 hour and 8-hour PK sample collection at the discretion of the investigator or study coordinator.

- Interview
  - Review of adverse events;
  - Review concomitant medications.
- Assessments
  - Measure and record height, weight, waist circumference, and calculate BMI z-score;
  - Obtain and record vital signs;
  - Perform a complete physical examination.
- Sample Collection
  - Collect fasting blood samples as indicated on the General Study Assessment Schedule;

- Collection of PK samples (T0) prior to dose, and at 0.5 hours (±2 minutes), 1-hour (±2 minutes), 1.5-hour (±2 minutes), 2-hour (±5 minutes), 4 (±5 minutes), 6 (±10 minutes) and 8 hours (± 10 minutes) post dose;
- Collect urine sample for UA and for urine pregnancy testing (as applicable and locally tested).

- Dosing and Compliance Check (collect carton previously dispensed at visit 1)
  - Conduct a pill count;
  - Review diary;
  - Administration of dose in the clinic. Dose will be administered with approximately 50 mL of water and check that study drug is swallowed.
- Instructions
  - Counselling regarding a diet and exercise regimen that should be maintained throughout the study.
  - Review dosing procedure and completion of dosing diary and dispense 1-month supply of study drug (refer to Appendix II).
  - Remind the patient not to take any dose of study medication the day of V4 before presenting to the clinic.

5.2.5. Visit 4/Week 4 (Day 30)

It is estimated the visit will take approximately 30 minutes to complete.

- Interview
  - Review of adverse events.
- Sample Collection
  - Collect 24-hour (± 10 minutes) post Day 29 dose PK blood sample.
- Dosing
  - Administration of dose in the clinic. Dose will be administered with approximately 50 mL of water and check that study drug is swallowed.
- Instructions
  - Review dosing procedure and completion of dosing diary and dispense 1-month supply of study drug (refer to Appendix II).
  - Remind the patient not to take any dose of study medication the day of V5 before presenting to the clinic.
  - Remind the parent/legal guardian/patient to present for Visit 5 in a fasted state (nothing to eat or drink (except water) for 10 hours prior to the visit).

5.2.6. Visit 5/Week 8 (Day 57 ±2 days)

It is estimated that the visit will take about 1 hour to complete.

- Interview
  - Review of adverse events;
  - Review concomitant medications.
- Assessments
  - Measure and record height, weight, waist circumference, and calculate BMI z-score;
  - Obtain and record vital signs;

- Perform a complete physical examination.

- Sample Collection
  - Collect fasting blood samples as indicated on the General Study Assessment Schedule;
  - Collect urine sample for UA and for urine pregnancy testing (as applicable and locally tested);
- Dosing and Compliance Check (collect the carton previously dispensed at visit 3)
  - Conduct a pill count;
  - Review diary;
  - Administration of dose in the clinic. Dose will be administered with approximately 50 mL of water and check that study drug is swallowed.
- Instructions
  - Counselling regarding a diet and exercise regimen that should be maintained throughout the study.
  - Review dosing procedure and completion of dosing diary and dispense 1-month supply of study drug (refer to Appendix II).
  - Remind the parent/legal guardian/patient to present for Visit 6 in a fasted state (nothing to eat or drink (except water) for 10 hours prior to the visit).
  - Remind the patient not to take any dose of study medication the day of V6.

5.2.7. Visit 6/EOT Week 12 (Day 85 ±2 days)

It is estimated that visit will take about 2 hours to complete.

- Interview
  - Review of adverse events;
  - Review concomitant medications;
- Assessments
  - Measure and record height, weight, waist circumference, and calculate BMI z-score;
  - Obtain and record vital sign;
  - Obtain 12-lead ECG;
  - Perform a complete physical examination.
- Patient and parent/legal guardian to self-complete the PedsQL™ questionnaire individually.
- Sample Collection
  - Collect fasting blood samples as indicated on the General Study Assessment Schedule;
  - Collect urine sample for UA and for urine pregnancy testing (as applicable and locally tested);
  - Collect PK samples approximately 24 hours after the last dose (dose taken on day 84).
- Compliance Check (collect the carton previously dispensed at visit 5)
  - Conduct a pill count;
  - Review diary;
  - Retrieve unused and used wallets of study drug.
- Instructions
  - Counselling regarding a diet and exercise regimen that should be maintained throughout the study (final visit).

- Remind the parent/legal guardian/patient to present for Visit 7 in a fasted state (nothing to eat or drink (except water) for 10 hours prior to the visit).

In case of early termination at any time after Visit 1 the next visit the patient will complete will be Visit 6/EOT procedures.

5.2.8. Visit 7/EOS Week 16 (Day 113 ±2 days)

It is estimated that visit will take about 2 hours to complete.

- Interview
  - Review of adverse events;
  - Review concomitant medications.
- Assessments
  - Measure and record height, weight, weight circumference, and calculate BMI z-score;
  - Obtain and record vital signs;
  - Perform a complete physical examination.
- Sample Collection
  - Collect fasting blood samples as indicated on the General Study Assessment Schedule;
  - Collect urine sample for UA and for urine pregnancy testing (as applicable and locally tested).

5.3. Other Visit

5.3.1. Retesting Screening Visit

Upon receipt of result from biological assessment done at Screening Visit 1, and in case a retesting is needed according to the selection criteria, an additional visit will be scheduled according to the recommended timeframe for retesting.

Permitted retest in case of abnormal value at Screening Visit 1 is:

- CPK: can be repeated prior to randomization (Day 1).

Any other retest deemed necessary by the investigator at any time during the study should be discussed with the study medical monitor.

5.3.2. Safety follow-up visit

If at V7/EOS any safety lab parameter is abnormal and at least 10% higher than the highest reported values obtained between SV1 and V1, an additional visit should be scheduled one month later to repeat those affected parameters.
The safety lab parameters are defined as hematology, coagulation biochemistry, lipids and inflammatory markers.

5.3.3. 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 5.2.2.

These solutions can be applied after Medical Monitor approval and depending on the investigator's judgment of each case and the patient/parent(s) '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 and parent(s) to check whether they agree 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.

5.3.3.1. *Safety and drug compliance procedures*

The following procedures will be performed if applicable for the visit via either a phone contact, or, if safe and possible, a direct visit to the patient:

- Check for AEs
- Collection of any lifestyle modifications
- Check concomitant/prior medication
- Check of compliance (review of dosing diary with the patient/parent(s))
- Physical examination if possible with a direct visit to the patient or using video (described in Section 6.2.1)
- Record vital signs, waist circumference and weight if possible with a direct visit to the patient (described in Section 6.2.1 and Section 6.2.2)

5.3.3.2. *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 and biochemistry testing.

If a direct visit to the patient is safe and possible, the appropriate lab parameters corresponding to the on-site study visit will be collected.

5.3.3.3. *Delivery of study treatment to the patient*

The study treatment can be shipped to the patient or delivered directly to the patient by the site study staff if safe and possible as per the site procedure.

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 7.7 and Section 7.8 once brought to the study site/study pharmacy.

5.3.3.4. *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.

5.4. Patient Withdrawal and Discontinuation

5.4.1. Early Termination

A patient or the patient's parent/legal guardian may withdraw the patient from treatment or from the study at any time at their request or may be withdrawn at any time at the discretion of the Investigator or Sponsor for safety, behavioral, or administrative reasons. Upon withdrawal, the study drug should be permanently discontinued.

5.4.1.1. *Discontinuation for Treatment*

A patient must be permanently discontinued from the study drug for any of the following reasons:

- The patient becomes pregnant;
- Allergic or adverse reaction to the study drug;
- Per section 6.3 of the protocol referring to Important specific biological considerations for patient discontinuation related to reported lab values;
- Clinically significant adverse event, which in the opinion of the Investigator, would put the patient at unnecessary risk if dosing was continued; or
- If a patient is discontinued from treatment at any time after Visit 1, they should complete the Visit 6/EOT visit and will be encouraged to return one month later for Visit 7/EOS visit.

5.4.1.2. *Discontinuation from Study*

A patient must be discontinued from the study drug and from the study for the following reason:

- The patient/parent/legal guardian withdraws consent. From the time consent is withdrawn, no additional data should be collected. However, the Sponsor may retain and continue to use data collected before such withdrawal of consent.

5.4.2. Replacement

Patient replacement will be at the discretion of the Sponsor.

5.4.3. Lost to Follow-up

A patient is considered to have been lost to follow-up if he/she [patient or parent/legal guardian] cannot be contacted by the Investigator (or designee). The Investigator (or designee) will document efforts to attempt to reach the patient twice by telephone and will send a certified letter before considering the patient lost to follow-up. The end of participation for a patient lost to follow-up is documented as the delivery date of the certified letter.

5.5. Safety Oversight

5.5.1. Investigator

The Principal Investigator must have access and be available to promptly review the results of all safety assessments (i.e., clinical laboratory testing), electrocardiogram (ECG) results, vital signs and adverse events (AEs) including application site assessment information throughout the study. Safety assessments must be promptly (should be within 48 hours of notification of event) entered into the Electronic Data Capture (EDC) system. Clinical laboratory data will be evaluated by the Principal Investigator and clinical relevance will be assessed for abnormal values and the assessment will be documented on the laboratory report. A copy of the reports will be maintained as part of the source documentation.

5.5.2. Data and Safety Monitoring Board

A DSMB will be established to monitor the progress of the study and to perform safety data reviews as designated in the DSMB charter, in order to protect patient welfare. The DSMB charter will define the role, responsibilities, rules and tasks, schedule, and format of meetings and data review and reporting requirements.

The DSMB considers study-specific data as well as relevant background knowledge about the disease, test agent, or patient population under study. The primary responsibilities of the DSMB are to 1) review and evaluate the accumulated study data for participant safety, study conduct and progress, and 2) make recommendations concerning the continuation (i.e. proceeding with enrollment of patients in cohort 2), modification, or termination of the trial. All DSMB discussions, decisions, and recommendations will be communicated promptly to the Sponsor as described in the DSMB charter.

The DSMB will consist of two independent clinicians with relevant expertise in related NAFLD/NASH pediatric clinical trials and 1 statistician with expertise in clinical trial and interim data analysis.

At minimum, safety data will be summarized by the statistician after every 5th patient completes visit 4 or available data at the end of each quarter (at approximately 3-month intervals), whichever comes first throughout the study. The DSMB will also review safety and PK data once 80% of the patients in Cohort 1 have completed through Visit 4. Enrollment in Cohort 2 will commence as recommended by the DSMB.

6. ASSESSMENTS

6.1. Efficacy and Safety Assessments

6.1.1. Biological Assessments

All blood samples for efficacy and/or for safety assessment will be analyzed by the central laboratory. The Laboratory Manual will outline the collection process and shipping requirements. Blood will be taken a total of 15 times over a 16-week period. On Days 29 and 30 blood samples will be collected 9 times over a 24-hour period. Refer to the Laboratory Manual for exact amounts of blood required for each test.

6.1.1.1. *Collection Procedure*

Blood sampling will be performed by trained personnel at each site. Use of diversional activities (E.g., cell phone or tablet) or use of a topical anesthetic (e.g., EMLA cream) should be considered in order to reduce pain associated with venipuncture. An indwelling catheter may be inserted for repeat sample collection, while to patient is in the clinic. The catheter should be flushed with saline between sampling.

6.1.1.2. *Reporting*

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

6.1.1.3. *Sample Retention*

Blood samples may be retained indefinitely by the Sponsor for future testing for the purpose of investigating the study drug's safety and effectiveness in support of future clinical research and/or to answer regulatory authority questions related to safety and effectiveness at the time of registration. Samples will only be identified by the patient number. Blood samples will not be shared with other research institutions for purposes outside of the protocol.

6.1.1.4. *Hematology and Coagulation Parameters*

The following parameters will be collected after fasting (nothing to eat or drink except water) for a minimum of 10 hours: Hemoglobin, hematocrit, red blood cells RBC), white blood cells (WBC) platelet count, differential count, reticulocyte count and prothrombin (PT) and international normalized ratio (INR).

6.1.1.5. *Pregnancy Test*

A pregnancy test is required for female patients of childbearing potential. Results must be negative at Screening Visit 1. Additionally, a urine pregnancy test (Clinical Laboratory Improvement Amendment - CLIA waived) will be done prior to Randomization (Visit 1) and at each study visit, with the exception of visit 4. Serum confirmation will be completed for all positive urine pregnancy tests.

6.1.1.6. *Serology*

All patients will be screened for HIV, hepatitis A antibody (anti-HAV), hepatitis B surface antigen (HBsAg), hepatitis C antibody (anti-HCV), and hepatitis E antibody (anti-HEV). Evaluation for HIV seropositivity will consist of enzyme-linked immunosorbent assay (ELISA) and, if positive, will be confirmed by the Bio Rad Multispot HIV-1/2 antibody differential test. Appropriate counseling will be made available to the patient in the event of a positive finding. Notification of state and federal authorities, as required by law, will be the responsibility of the Investigator.

6.1.1.7. *Other Parameters for Eligibility Assessment*

In case patient hasn't been screened for the following parameters: Antimitochondrial Antibody (AMA), Alpha-1-Antitrypsin Phenotype, Ceruloplasmin, Ferritin, Transferrin Saturation (Serum Iron, Total Iron Binding Capacity), these parameters will be tested centrally at screening visit 1.

6.1.1.8. *Biochemistry*

The following parameters will be collected after fasting (nothing to eat or drink except water) for a minimum of 10 hours: creatinine, creatinine clearance (eGFR), total proteins, albumin, electrolytes (sodium, potassium, chloride, calcium), uric acid, urea, creatine phosphokinase (CPK), AST, ALT, gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP), total and conjugated bilirubin, high sensitivity C-reactive protein (hsCRP), fasting plasma glucose, fasting insulin, homeostatic model assessment of insulin resistance (HOMA-IR), fructosamine, C-peptide, free fatty acids (FFA), hemoglobin A1c (HbA1c), thyroid stimulating hormone (TSH). Cystatin C, eGFR from Cystatin C.

6.1.1.9. *Lipid Profile*

The following parameters will be collected after fasting (nothing to eat or drink accept water) for a minimum of 10 hours: total cholesterol [TC], non high-density lipoprotein cholesterol [non-HDL-C], HDL-C, low-density lipoprotein-cholesterol [LDL-C], triglycerides [TG]), calculated very low-density lipoprotein (VLDL-C), apolipoprotein A-I (ApoAI), and Apolipoprotein B (ApoB)).

6.1.1.10. *Urinalysis*

A urine sample will be collected and a macroscopic urinalysis (by urine dipstick) will be done by Medpace Reference Laboratory. The following test will be done centrally via this method, specific gravity, pH,

protein, glucose, ketones, bilirubin, urobilinogen, blood, nitrite and leukocytes. Should any result from the urine dip stick be positive, a urine microscopic exam will be performed. Other urine parameters will be tested by the central laboratory include: α1 microglobulin, β-NAG, N-Gal, albumin and creatinine.

6.1.1.11. *Liver Markers*

The following parameters will be collected after fasting (nothing to eat or drink except water) for a minimum of 10 hours: CK18 (M65 & M30), adiponectin, ferritin, FGF19 & FGF21, α2 macroglobulin, hyaluronic acid, PIIINP, TIMP-1.

6.1.1.12. *Inflammatory Markers*

The following parameters will be collected after fasting (nothing to eat or drink except water) for a minimum of 10 hours: fibrinogen, haptoglobin, TNF-α, IL-6, PAI-1

6.1.1.13. *Other Parameters*

Additional tubes of serum will be collected for the purpose of research about pediatric NASH and biomarker.

6.1.2. Pharmacokinetics Evaluation

6.1.2.1. *Description of Pharmacokinetic Evaluation Parameters*

Pre-dose PK sample will be collected prior to first dose administration on Day 1 (Visit 1).

Pharmacokinetic samples will be collected on Day 29 (± 2 days) at T0 (prior to morning dose, 0.5 (±2 minutes), 1 (±2 minutes), 1.5 (±2 minutes), 2 (±5 minutes), 4 (±5 minutes), 6 (±10 minutes), 8 (±10 minutes) and 24 hours (±10 minutes) and on Day 85 (± 2 days) approximately 24 hours (±10 minutes) after the last study drug administration to determine PK parameters for assessment of elafibranor and its active metabolite GFT1007, at steady state.

Details regarding collection, processing, storage and shipment will be described in the Laboratory Manual.

6.1.2.2. *Pharmacokinetic Analysis*

The PK analysis will be conducted at Eurofins ADME BIOANALYSES (75A Avenue de Pascalet 30310 Vergèze FRANCE) in compliance with the Standard Operating Procedures in use at Eurofins ADME BIOANALYSES.

Elafibranor and GFT1007 will be assayed by measuring concentrations according to an analytical method previously developed and validated by Eurofins ADME BIOANALYSES.

6.1.2.3. *Pharmacokinetic Blood Sampling Timepoints*

Blood sampling will be performed for elafibranor and main active metabolite GFT1007 plasma concentration measurements at the following timepoints:

- Visit 1/Day 1: Pre dose;
- Visit 3/Day 29 (± 2 days): T0 (prior to morning dose under fasting conditions), 0.5 (±2 minutes), 1 (±2 minutes), 1.5 (±2 minutes), 2 (±5 minutes), 4 (±5 minutes), 6 (±10 minutes), 8 (±10 minutes);
- Visit 4/Day 30: 24 hours (±10 minutes) post dose administered at V3 (and prior to next dose of study drug);

- Visit 6/Day 85 (± 2 days): PK sample approximately 24 hours (±10 minutes) after last study drug administration.

6.1.2.4. *Pharmacokinetic Blood Handling Procedures*

Blood samples will be collected into 1mL lithium heparin tubes protected from light with foil and plasma will be separated in a refrigerated centrifuge (ca.4°c) at 1500 g for 15 minutes and a volume of 250µl will be dispensed in a polypropylene opaque tube for both aliquots 1 and 2.

The plasma will be stored at -20°c ±5°C at the site facilities.

Thereafter, the plasma will be transported in dry ice, first to the central laboratory where they will be stored at -20°C ±5°C until shipped to Eurofins ADME BIOANALYSE for analysis.

6.2. Other Safety Assessments and On-going Safety Monitoring

6.2.1. Physical Examination

A physical examination will be performed at each visit. The physical examination will include an examination of general appearance, skin, eyes, ears, nose, throat, neck/thyroid, lungs, heart, upper/lower extremities, lymph nodes, abdomen, musculoskeletal system and basic neurological assessment. Additional systems will be evaluated as needed. Physical exam findings must be recorded in the source documentation and include the date and name of the individual conducting the examination. Physical examinations must be performed by an individual licensed to conduct standard physical examinations.

6.2.2. Vital Signs

Blood pressure [BP (mmHg)] and pulse rate [PR (BPM)] will be measured at each visit (with the exception of Visit 4) according to the "Recommendations for Blood Pressure Measurement in Humans and Experimental Animals" published in an AHA scientific statement.

It is important that vital signs be taken before any invasive procedures (e.g., venipuncture). Each measurement should be recorded in the source document and recorded in the electronic case report form (eCRF).

Important Points for Clinical Blood Pressure Measurement:

- The patient should be seated comfortably with the back supported and the upper arm bared without constrictive clothing. The legs should not be crossed. It is recommended the same arm be used for the collection of blood pressure readings throughout the patient's participation.

- 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 Blood Pressure (SBP) and Diastolic Blood Pressure (DBP) will be measured after 5 minutes of rest in the seated 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. 12-Lead ECG

All investigative sites will perform ECG using a calibrated ECG machine. Site personnel must assess the quality of the ECG while the patient is still at the investigative site in the event that additional ECGs need to be performed (i.e., if artifact is present).

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

For younger children, the parent/legal guardian may need to practice, prior to the study visit, lying still. Suggest use of a timer to help the child understand how long to hold still. If possible, have the patient rest quietly for at least 10 minutes. Refer to Study Procedure Manual for additional details regarding data collection and transmission.

6.2.4. Pediatric Quality of Life (PedsQL™)

The child, adolescent and parent/legal guardian PedsQL™ (Version 4.0) Generic Core Scales will be used in this study. The scale validated for use in the pediatric populations; child version for 8-12 years of age and teen version for 13 to 18 years of age and a parent version for each respective age group. It is composed of 23 items comprising 4 dimensions. A copy of the scales and instructions for scoring will be provided to the site. The Sponsor has secured the required licensing for use of the scale in this study. The PedsQL™ (Version 4.0) will be completed on paper by the patient and by a parent/legal guardian individually. This information will then be entered on the eCRF page by study site staff. The patient/ parent or legal guardian will complete the same version of the questionnaire throughout the study.

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 marked increase in muscle CPK values higher than 2 x ULN, the patient must be discontinued from study drug immediately and followed up as described in Section 5.4.1.1.

If at any visit during the treatment periods, a patient experiences marked increase in muscle CPK values >2x ULN without symptoms or if associated with vigorous exercise, an additional visit and test should be done within approximately 48 to 72 hours. If during that visit CPK elevations persist, the patient must be discontinued from study treatment immediately and followed up as described in Section 5.4.1.1.

6.3.2. Liver Function Monitoring

- Increase in aminotransferase (AT) of <3 x baseline value: no additional action required, schedule next visit as per assessment schedule.
- Liver function monitoring requirements for all patients with increased in AT > 3x baseline value:
    - Increase in AT of >3 x baseline value but less than 10 x ULN: retest after 48 to 72 hours.
    - AT remains >3 x baseline value and <5 x the baseline, or 10 x ULN: continue the drug with close serial monitoring (once a week).
    - AT increases >5 x baseline value will lead to permanent discontinuation of the patient from study drug and schedule EOT Visit (refer to Section 5.2.7).
    - An increase of AT >10 x ULN will lead to immediate permanent discontinuation of the patient from study drug, and scheduling of EOT visit (refer to Section 5.2.7).

Patients will permanently discontinue from study drug (refer to Section 5.2.8 and 5.4.1.1) if at any visit during the treatment periods they exhibit any of the following:

- Increase in AT >3 x baseline value AND increase in total bilirubin >2 ULN;
- Increase in AT >3 x baseline value AND increase in INR>1.5; or
- Increase in AT >3 x baseline value AND fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).

6.3.3. Renal Function Monitoring

- Decrease in eGFR of 15ml/min/1.73m² or more compared to baseline value associated with cystatin C > ULN: retest of serum creatinine, cystatin C and eGFR within approximately 48 to 72 hours.
- If decrease in eGFR and increase in cystatin C persists, permanent discontinuation from study drug will be considered and discussed with the Medical Monitor(see Section 5.2.8 and 5.4.1.1).
- In case of an increase of creatinine or Cystatin C >20% from baseline: retest every two weeks until two consecutive results are <20% from baseline. A retest visit should be considered and discussed with the Medical Monitor if no protocol required visit is planned within the next two weeks.
- Decrease of eGFR at a value less than 60 ml/min/1.73m²: permanently discontinue patient from study drug and schedule EOT Visit (refer to Section 5.2.7).

6.3.4. Additional Monitoring

- Decrease in haemoglobin greater than 2mg/dL from baseline: retest within 48 to 72 hours.
- If haemoglobin decline is persistent or worsening and unexplained by other causes, permanently discontinue patient from study drug and schedule EOT Visit (refer to Section 5.2.7).

6.4. Guidance for Investigators

6.4.1. Summary of Safety Data

6.4.1.1. *Non-Serious Adverse Drug Reactions*

For all completed studies to date with repeated administration of elafibranor (at least 14 days) from 80 mg/day up to 300 mg/day (MTD), numbers and percentages of frequency of adverse drug reactions (ADR, adverse events reported by investigators as possibly related or related to study drug) have been calculated compared to the total number of subjects treated with elafibranor and the total number of subjects treated with placebo.

Only non-serious adverse reactions with frequency > 1% are considered for reporting. Given the small numbers for each adverse reaction identified with a frequency >1%, an imbalance in frequency of occurrence compared to placebo is reported when the relative delta is ≥ 30%.

The common non-serious adverse drug reactions reported with repeated doses of at least 80 mg elafibranor per day are thus summarized in Table 1.

Among the non-serious adverse reactions, the most frequent were gastro-intestinal disorders and general disorders. The first ones in term of frequency consisted mostly of diarrhea and vomiting. For general disorders, the main symptoms were fatigue / asthenia.

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 Modification of Diet in Renal Disease (MDRD) based on creatinine). Myalgia, decrease of appetite, and rash were also reported in more than 1% of patients but remain limited.

Table 1 Overview of the Common Non-Serious Adverse Reactions (>1% of Patients Treated with Elafibranor) by System Organ Class 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 (2.9%)
	Vomiting	Mild to moderate	9 (1.5%)
General disorders and administration site conditions	Fatigue / Asthenia	Mild to moderate	17 (2.9%)
Investigations	Hepatic enzymes increased (mainly transaminases)	Mild to severe	11 (1.9%)
	Blood creatine phosphokinase increased	Mild to moderate	6 (1.0%)
Musculoskeletal and connective tissue disorders	Myalgia	Mild to severe	9 (1.5%)
Metabolism & nutrition disorders	Decreased appetite	Mild to severe	9 (1.5%)
Skin and subcutaneous tissue disorders	Rash	Mild to moderate	8 (1.4%)
Renal and urinary disorders	Renal failure/impairment	Mild to moderate	7 (1.2%)

6.4.1.2. *Serious Adverse Drug Reactions*

The 9 serious adverse reactions (serious adverse events reported by investigators as possibly related or related to study drug) reported in 6 patients treated with elafibranor in completed clinical studies are summarized in Table 2.

Table 2 Overview of Suspected Unexpected Serious Adverse Reactions (SUSARs) by System Organ Class Reported in Completed Elafibranor Clinical Studies

System Organ Class	Adverse Reaction	Severity	Number of cases (Frequency %)
Cardiac disorders	Atrial fibrillation	Moderate	1 (0.12%)
Gastrointestinal disorders	Acute pancreatitis	Mild	1 (0.12%)
	Pancreatitis*	Moderate	1 (0.12%)
Hepatobiliary disorders	Acute cholecystitis*	Moderate	1 (0.12%)
Nervous system disorders	Ataxia**	Moderate	1 (0.12%)
	Tremor**	Moderate	1 (0.12%)
	Involuntary muscle contractions**	Moderate	1 (0.12%)
	Parkinson's disease	Moderate	1 (0.12%)
Pregnancy, puerperium and perinatal conditions	Spontaneous abortion	Mild	1 (0.12%)

*all in one patient
**all in one patient

All 9 serious adverse reactions were reported as suspected unexpected serious adverse reactions (SUSARs). However, 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, these events were considered as having no reasonable causal relationship to elafibranor by the Sponsor.

For the other cases of possibly related serious adverse events (SAEs), the causality assessment to elafibranor was considered as having a reasonable possibility both by the investigator and by the Sponsor as there was no way to rule out a relationship to study drug.

6.4.2. Potential Risks

In toxicology studies, the only consistent safety concern was 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 humans [Cattley *et al.*, 1998]. Elafibranor did not show any of the known PPARγ-related concerns such as excess in weight gain, hemodilution, edema, cardiomegaly, adiponectin induction, or urinary bladder carcinoma.

Regarding specific monitoring, although no signal for increase in CPK has been observed in 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 an increase of creatinine, which was observed in Phase 2 trials with elafibranor, and corresponded to an increase of 5-10% that was reversible at end of treatment. This should also be monitored in clinical trials.

Liver enzymes are also monitored in clinical trials, with specific attention paid to drug-induced liver injury.

Based on the findings of non-clinical 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 women of childbearing potential require 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 within the Study General Assessment schedule.

6.4.3. Risk Benefit Analysis

Clinical data have confirmed the potential beneficial effect of elafibranor in adult subjects with NASH.

Phase 2 studies in subjects with cardiometabolic disorders and NASH have demonstrated consistent reductions in ALP compared to placebo. The reduction in ALP was associated with relevant reductions in markers of liver injury such as GGT and ALT and in inflammatory markers. These data are encouraging to consider elafibranor as a potential drug candidate to treat PBC.

In addition, the Phase 2b trial in NASH patients 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-C, 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, these studies have highlighted the good safety profile of elafibranor and no major safety concerns have been raised.

Based on the cumulative experience gathered to date, gastrointestinal 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 the clinical trials as this has been observed in Phase 2 studies to date and is a known PPARα agonist effect. Elevation of transaminases should also be monitored as well as drug-induced liver injury. In the absence of 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.

In conclusion, the safety data and the current knowledge on elafibranor confirm the favorable balance between anticipated efficacy/benefits and risks.

7. TREATMENTS

7.1. Description of Study Drug

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 80 mg or 120 mg white to off-white round coated tablets (of different size) with no printed inscription. The tablet contains elafibranor and inactive ingredients (microcrystalline cellulose, povidone, croscarmellose, anhydrous colloidal silica, magnesium stearate, opadry II HP 85F18422).

The safety of elafibranor is supported by non-clinical toxicity data (adult and juvenile toxicity studies) for the youngest/lightest patients at the two dosage strengths for the expected duration of treatment.

The excipients used in the manufacture of elafibranor 80 mg and 120 mg coated tablets have been commonly used in drug oral forms for decades both in adult and pediatric formulations. All of them are compliant with the European and US Pharmacopeia (including all components of the coating) (refer to Table 3).

Elafibranor tablets formulation does not contain any excipient with known adverse effects such as preservatives, coloring agents, sugars, and sweeteners.

Table 3 Formulation of Elafibranor 120 mg Coated Tablet and Elafibranor 80 mg Coated Tablet

Excipient	% w/w	Elafibranor 120 mg Tablet	Elafibranor 80 mg Tablet
		mg/tablet	mg/tablet
Core tablet			
Elafibranor	38.217	120.0	80.0
Microcrystalline cellulose	45.669	143.4	95.6
Povidone	4.777	15.0	10.0
Croscarmellose	5.732	18.0	12.0
Anhydrous colloidal silica	0.191	0.6	0.4
Magnesium stearate	0.955	3.0	2.0
Coating			
Opadry II HP 85F18422®	4.459	14.0	9.3
Purified Water	-	-	-
Total fill weight (mg)	100.0	314.0	209.3
Dosage strength	-	120.0	80.0

For additional information see Investigator's Brochure.

7.2. Packaging and Labeling

7.2.1. Packaging

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.

For elafibranor 120 mg, blisters containing 8 tablets each, will be packed in child proof wallets.

- Each child proof wallet will contain 1 blister.
- Five wallets will be packaged inside a carton.

For elafibranor 80 mg blisters containing 7 tablets each, will be packed in child proof wallets.

- Each child proof wallet will contain 1 blister.
- Five 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 labelled 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."

7.3. Storage Conditions

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

7.4. Dispensing and Administration of treatment

Treatment (dose group) assignment will be provided via the central randomization procedure. The drug inventory is open label and will be distinctly labelled with respect to dose level. Study personnel will select the next available corresponding kit (1-month supply) in inventory at the appropriate dose level and will immediately record the assigned kit in the eCRF. Patients will be informed to take one tablet per day of elafibranor 80 mg or 120 mg orally before breakfast with a glass of water each morning.

7.5. Procedure for Blinding

Not applicable

7.6. Procedure for Unblinding

Not applicable

7.7. Study Drug Compliance

From Visit 1 and at each subsequent visit while the patient is being treated with study drug up to the EOT visit, the patient will be instructed to bring back all used and unused cartons and wallets containing blisters. Compliance will be checked by the Investigator or their designee during those visits and recorded in the eCRF.

If treatment is interrupted, whatever the cause, duration and reason for the interruption should be documented in the dosing diary and on the source documentation.

7.8. 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, all treatments (used or unused) may be destroyed on site per acceptable site Drug Destruction Standard Operating Procedure or the Drug Distribution Centre will organize the retrieval of all treatments (used or unused) and will proceed to their destruction after the Sponsor provides written authorization.

7.9. Other Medication

7.9.1. 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 (Appendix III)

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 3 months prior to screening) and information should be communicated to the Medical Monitor.

This includes drugs used on a chronic as well as on an 'as needed' basis.

7.9.2. Non-Permitted Medication

The following medications are not allowed:

- Thiazolidinediones (glitazones [pioglitazone & rosiglitazone]): From 3 months (12 weeks) prior to Screening Visit 1 (SV1) up to End of Study (Visit 7);
- Fibrates: From 2 months (8 weeks) prior to Screening Visit 1 up to End of Study (Visit 7);
- Indomethacin: From Randomization (V1/Day 1) to End of Treatment (V6).

Chronic use of the following medication is not permitted):

- Methotrexate, tamoxifen, chronic systemic glucocorticoid, tetracycline, valproic acid, salicylates:
- From 12 months prior to screening (Screening Visit 1) up to Randomization (Visit 1): chronic use defined as treatment longer than 3 consecutive months.

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.

7.9.3. Permitted Medication Under Conditions

The following medications are permitted under the condition of no qualitative change and stable dose for 3 months prior to Screening Visit 1 up to Randomization (Visit 1/Day 1):

- Statins, ezetimibe, and other nonfibrate lipid lowering medications;
- Anti-diabetic as insulin, metformin, Gliptins, Sulfonylureas, glucagon-like peptide 1 (GLP-1) agonist, sodium/glucose cotransporter 2 (SGLT2) inhibitor;
- Medication to treat NAFLD/NASH such as Vitamin E, ursodeoxycholic acid, PUFAs.

During the study (from V1 to V7), qualitative change and dose change should be avoided as much as possible. All qualitative and dose changes must be captured in the source and eCRF.

Chronic use (defined as treatment longer than 2 consecutive weeks) of the following medication should be avoided if possible, from V1 to V7:

- Methotrexate, tamoxifen, chronic systemic glucocorticoid, tetracycline, valproic acid, salicylates.

8. ADVERSE EVENT / SERIOUS ADVERSE EVENT REPORTING

8.1. Definitions

8.1.1. Adverse Event (AE)

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 Food and Drug Administration (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 a medical condition is 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.

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 (SAE)

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); or
- Is another medically important condition (see Section 8.1.2.4).

In addition, any illnesses reported before starting active treatment that have worsened after ICF signed or AE meeting the criteria of seriousness (as defined above) 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. *In-Patient or Prolonged Hospitalization*

An inpatient hospitalization or prolongation of a hospitalization means that the patient stays overnight in the hospital. 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.

- 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 Condition*

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

- Death is an outcome of an AE, not an AE.
- 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 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 causally related to an investigational medicinal product. A serious adverse drug reaction (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 AEs have occurred at each visit from the date of consent through the EOS visit (or 30 days after the last drug intake whichever is later). 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 and 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 study drug 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 the EOS visit (or 30 days after last drug intake, whichever is later). 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 EOS visit (or 30 days after last drug intake, whichever is later).

8.3.2. Reporting a Serious Adverse Event

Serious AE reporting begins from signature of the patient ICF and ends at the EOS visit (or 30 days after last drug intake, whichever is later). 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.

Investigators must notify, by fax or e-mail, the Sponsor designated representative SGS Life Sciences Services Medical Affairs 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 SGS Life Science Services MEDICAL AFFAIRS AT THE FOLLOWING FAX NUMBERS:

FAX numbers: +32 (0)15 29 93 94 or 1-800-746-6618

Contact Person: SGS Life Science Services Medical Affairs Department

E-mail: be.life.saefax-ma@sgs.com

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 SGS Life Science Services Medical Affairs 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 relevant to the reported SAE 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 SGS Life Science Services Medical Affairs 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 concerned 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
- 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 concerned Competent Authority(ies) 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, even if this goes beyond the EOS visit.

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 SGS Life Science Services Medical Affairs by faxing a completed pregnancy form within 24 hours of his/her knowledge of the pregnancy.

Pregnancies of female partners of male patients exposed to study medication should also be reported to SGS Life Science Services Medical Affairs 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 8.6).

8.6.3. Misuse

This refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol. In case of any potential risk to patient safety, would be reported as appropriate (see Section 8.6).

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 highest dose of the protocol. 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

9.1. Randomization and Treatment Assignment

Number of Randomized Patients (planned): A total of 20 patients will be enrolled across the two cohorts.

- Cohort 1: ≥12 to ≤17 years of age. A total of approximately 12 patients will be randomized in this cohort.
- Cohort 2: ≥8 to ≤11 years of age. A total of approximately 8 patients will be randomized in this cohort. Enrollment in this cohort will not start until 80% of the patients in cohort 1 have been evaluated through Visit 4 by the Data Safety Monitoring Board.

Patients will be randomized 1:1 to receive either dose (80 or 120 mg).

Considering that at least 4 patients ≥12 to ≤17 years of age and at least 2 patients ≥8 to ≤11 years of age with fibrosis stage 2 or 3 will be enrolled and to achieve balance between dosing groups according to the fibrosis severity, randomization will be stratified within each cohort based upon screening fibrosis severity stage (stratum 1:fibrosis stage 0 to 1 and stratum 2: fibrosis stage 2 to 3).

The randomization procedure will be further described in the Study Procedure Manual.

9.2. Endpoints

9.2.1. Primary Endpoint

Plasma concentrations of elafibranor and its active metabolite GFT1007.

9.2.2. Secondary Endpoints

9.2.2.1. *Efficacy*

- Change from baseline in serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), and alkaline phosphatase (ALP) and other liver markers;
- Change from baseline in serum lipid parameters;
- Change from baseline in glucose homeostasis makers (Fasting plasma glucose, Homeostatic Model Assessment of Insulin Resistance [HOMA-IR] and fasting insulin);

- Change from baseline in body weight and BMI z-score;
- Change from baseline in waist circumference;
- Change from baseline in inflammatory markers;
- Change from baseline in pediatric quality of life (PedsQL™) score.

9.2.2.2. *Safety*

- Incidence and severity of treatment emergent adverse events (TEAEs) and their relationship to study drug;
- Incidence of clinically meaningful changes from baseline in safety laboratory parameters, physical examination, ECG and vital signs.

9.2.3. Exploratory Endpoint

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9.3. Sample Size Estimate

The primary objective of this study is to characterize individual PK parameters in children and adolescents 8 to 17 years of age (inclusive), by collecting rich PK samples to support noncompartmental analysis. Inter-subject variability of PK parameters in adults was low to moderate (coefficient of variation [CV]% ranged from 23.3% to 68.3%). Assuming a similar degree of variability in pediatric population, a sample size of 20 patients is set to target a 95% CI [confidence interval] within 60% and 140% of the geometric mean estimates of clearance and volume of distribution for elafibranor with at least 80% power (Wang *et al.*, 2012). Additionally, 20 patients should be sufficient to evaluate the safety and tolerability and explore the responsiveness (efficacy) of once daily oral dosing of 80 mg and 120 mg of elafibranor for up to 12 weeks.

9.4. Analysis Sets

Three populations will be used for analysis: safety, PK and intent-to-treat. The definition of these populations are as follows:

- Safety Population: All patients who received at least one dose of study drug and have at least one post-baseline safety assessment.
- Pharmacokinetic Population: All patients who received at least one dose of study drug, do not have protocol deviations or adverse events which may significantly affect PK, and have at least one post-dose PK sample.
- Intent-to-Treat (ITT) Population: All randomised patients who received at least one dose of study drug.

PK and safety data will be analysed based on the safety population. Efficacy data will be analysed based on the ITT population.

9.5. Analysis of Primary Endpoint

Individual plasma concentrations for elafibranor and its active metabolite GFT1007, will be summarized descriptively (i.e., number of observations, arithmetic mean, SD, CV%, median, minimum and maximum, geometric mean and CV% Geometric Mean by planned time points for each dose group. Individual plasma concentration-time profiles of elafibranor will be plotted on both linear and semi-logarithmic scales. Mean values over time by dose plots will also be presented graphically.

Pharmacokinetic parameters of elafibranor and GFT1007 will be estimated using NCA methods in Phoenix WinNonlin 8.0 or higher, using actual elapsed time from dosing. Plasma concentrations equal to or greater than the qualified lower limit of the assay (LOQ) will be used in the pharmacokinetic analysis. The following calculated PK parameters will include, but not limited to:

- Maximum concentration (C_{max});
- Time to maximum concentration (T_{max});
- Area under the plasma concentration time curve over 24 hours ($AUC_{[0-24]}$);
- Trough concentrations in plasma (C_{trough}).

The analysis plan will be further detailed in the PK Statistical Analysis Plan (PK-SAP).

9.6. Other Statistical Analysis

9.6.1. Safety

Safety evaluations will consist of adverse events (AEs), physical examinations, vital signs, ECGs, and laboratory measurements (hematology, coagulation parameters, biochemistry, and urinalysis). Full details will be specified in the SAP. A general description of the planned analysis is as follows:

- Laboratory parameters will be descriptively summarized (mean, SD, median, minimum, maximum) by dose group, for values at each visit and for changes from baseline at each subsequent visit. In addition, at each post baseline visit, parameter status (low, normal, high) will also be summarized as shift tables vs. baseline status.
- Vital signs will be summarized similarly as for laboratory parameters but without shift tables.
- Descriptive statistics and frequency tables will be prepared as appropriate for physical examinations, vital signs and ECG.
- Adverse Events
    - AEs descriptions will be mapped to standard terms according to the Medical Dictionary for Regulatory Activity (MedDRA).
    - AEs that start prior to first study drug dose and that worsen after, and the AEs that start on or after first study drug dose will be considered a treatment emergent adverse event (TEAE).
    - The number of events, the number and proportion of patients reporting at least one event will be tabulated overall and by severity. Each patient will be counted only once according to the worst severity reported over the treatment period.
    - Separate tables will be constructed by dose group and overall for (a) all reported TEAEs, (b) protocol treatment related TEAEs, (c) serious TEAEs, and (d) TEAEs leading to protocol treatment discontinuation.
    - The non TEAEs will be listed separately and will not be included in the AE tabulations.
- Concomitant medications will be mapped according to the World Health Organization (WHO) Drug Dictionary (WHODD) and will be presented in data listings.

9.6.2. Efficacy

- Descriptive summaries will be provided by dose group for the efficacy endpoints (liver markers, inflammatory markers, lipids, biochemistry parameters and liver function [e.g., ALT, AST, CPK, GGT, ALP], glucose homeostasis parameters (fasting plasma glucose, HOMA-IR and fasting insulin), body weight, BMI z-score, waist circumference and PedsQL™). Value at each visit and change from baseline will be summarized by dose group, and by age group and overall.

- Descriptive statistics for continuous variables will be number of patients, mean, SD, median, minimum and maximum and for categorical variables, frequency counts and percentages by dose group, and by age group and overall.

- If appropriate, shift tables vs. baseline status will be provided by dose group and by age group and overall, to describe change over time depending on relevant thresholds.

- Missing efficacy data will not be imputed for any analyses. The SAP will contain full details.

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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 CRFs 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 CRFs, 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 code of federal regulations (CFR) at 21 CFR Part 11.

All patient data generated during the study will be recorded in the eCRF. 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, approve and date each completed CRF electronically; the Investigator's validation serving as attestation of the Investigator's responsibility for ensuring that all clinical and laboratory data entered on the eCRF are complete, accurate and authentic.

Should a correction be made, the corrected information will be recorded on the eCRF by the authorized person and explained (if necessary). All corrected data will be tracked electronically 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/assent, visit dates, administration of study medication, Adverse Events (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 study drug. 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) 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 Investigator's Brochure, 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 the CRO 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 Standard Operating Procedures 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.

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, including interim monitoring visit reports will be reported and archived in the Trial Master File.

11.2. 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 manager from the Sponsor or 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. 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), 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.

12.2. Institutional Review Board/Independent Ethics Committee (IRB/IEC)

The GCP guidelines and the US CFR Title 21 Section 56 (21 CFR 56) require that approval must be obtained from an Institutional Review Board/ Independent Ethics Committee (IRB/IEC) prior to participation of human patients in research studies. Prior to the study onset, the protocol, ICF, assent, 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 one year) and a Study Progress Report following the completion, termination, or discontinuation of the Investigator's participation in the study.

12.3. Competent Authority

In the same way, 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.

12.4. Informed Consent

12.4.1. General Provisions

Informed consent will be obtained in accordance with the Declaration of Helsinki, ICH GCP, US Code of Federal Regulations for Protection of Human Subjects (21 CFR 50.25[a,b], CFR 50.27, and CFR Part 56, Subpart A), HIPAA (if applicable), and local regulations.

The Investigator (or designee) will prepare the Informed Consent Form, Assent and HIPAA authorization, as applicable, and provide the documents to the Sponsor or designee for approval prior to submission to the IRB/IEC. The consent/assent forms generated by the Investigator must be acceptable to the Sponsor and be approved by the IRB/IEC. The written consent document will embody the elements of informed consent as described in the International Conference on Harmonization and will also comply with local regulations. The Investigator will send an IRB/IEC-approved copy of the Informed Consent Form and Assent Form to the Sponsor (or designee) for the study file.

A properly executed, written, informed consent will be obtained from the patient's legally authorized representative (parent(s) or legal guardian(s)) prior to entering the patient into the trial and conducting any Screening procedures. Information should be given in both oral and written form and study patients and their parent(s)/legally authorized representative(s) must be given ample opportunity to inquire about details of the study. In accordance with the requirements of the approving IRB/IEC, assent from the study patient will also be obtained. A copy of the signed consent form (and assent) will be given to the study patient or legal representative of the study patient and the original will be maintained with the study patient's records.

12.4.2. Written Parental/Legal Guardian Consent

Adequate provisions must be made for soliciting the permission of the child's (less than 18 years of age) parent(s) or legal guardian. If a patient turns 18 years of age during the course of the study, written informed consent will be obtained from the patient.

The process for obtaining oral and/or written consent for children and adolescents is similar to that of obtaining consent for adults. An effective informed consent process involves at minimum these elements:

- Conducting the process in a manner and location that ensures privacy;
- Giving adequate information about the study in a language understandable to the parent/legal guardian and child/adolescent;

- Providing adequate opportunity for the parent/legal guardian and child to consider all options;
- Responding to the parent(s)/legal guardian(s) and child's questions;
- Ensuring the parent/legal guardian and child has understood the information provided;
- Obtaining the parent/legal guardian and child voluntary agreement to participate, and
- Continuing to provide information as the parent(s)/legal guardian(s), child, or research requires.

12.4.3. When Parents/Legal Guardian Disagree

If there are two parents/legal guardians available to give permission but they disagree about allowing their child to participate in the study, the child may not be enrolled unless that disagreement can be resolved. This applies to all permissible categories, even if only one parent or legal guardian's signature is required, when both parents/guardians are involved in the decision, they must agree for the child to be enrolled. If a parent or legal guardian who was not involved or available for the original consent later becomes involved or available, the two parents/legal guardians must then agree.

12.4.4. Assent

The Investigator should carefully consider and propose adequate provisions for obtaining assent of children and adolescents prior to their participating in research. In general assent is usually obtained from a child ≥ 7 years of age, however the approving IRB/IEC will determine whether or how assent will be obtained. The child should be provided with essential information and asked if they wish to participate in the research study.

12.4.5. Documenting the Consent/Assent Process

Consent/Assent MUST be obtained and documented PRIOR to initiation of any study procedures. The Investigator or his/her approved designee must explain the nature of the study and associated risks to the parent(s)/legal guardian and study patient. The date/time that the ICF and Assent is signed, a brief description of the consent/assent process (e.g., questions asked by the patient), and the name of the individual who obtained consent/assent will be recorded in the source record. A copy of the signed and dated ICF and Assent should be provided to the parent(s)/legal guardian(s). Depending on the approving IRB/IEC and local requirements, an assent form may be included as part of the consent and may or may not be required to be signed by the child. Investigators must adhere to their local requirements for proper documentation of consent/assent. A summary of assent procedures for execution of this study must be maintained in the Investigator Essential Regulatory File. It is the responsibility of the Investigator to ensure that any individual delegated the responsibility for obtaining consent/assent are familiar and adhere to the applicable consent/assent requirements.

12.5. 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 Clinical Trial Agreement.

12.6. Retained Blood Samples

Blood samples collected during the study for biological assessments may be retained for future testing as necessary. Patient confidentiality will be maintained and only the site and patient number will identify the sample. No other linked or identifying information is maintained by the Sponsor.

12.7. Definition of the End of the Research

End of the research corresponds to the end of participation of the last patient participating in the research and to the last close-out of study sites.

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

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.

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 eCRFs, 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 Institutional Review Board/Independent Ethics Committee (IRB/IEC) and the Competent Authority (if applicable) 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 eCRFs (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. REFERENCE LIST

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16. APPENDICES

16.1. Appendix I – World Medical Association Declaration of Helsinki

ETHICAL PRINCIPLES FOR MEDICAL RESEARCH INVOLVING HUMAN SUBJECTS - WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

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

16.1.1. 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.

16.1.2. 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.

16.1.3. 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.

16.1.4. 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.

16.1.5. 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.

16.1.6. 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.

16.1.7. Privacy and Confidentiality

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

16.1.8. 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.

16.1.9. 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.

16.1.10. 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.

16.1.11. 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.

16.1.12. 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 – Dosing Diary (Sample)

GFT505E-218-1 Dosing Diary
(INFORMATION TO BE COMPLETED BY PARENT/GUARDIAN/SC)

Patient ID # _____

	Study Day	Day of Week/ and Date Due (completed by study site)	Time of Morning Dose	Comments	Parent/Guardian/SC Dose Verification (signature)
Week 0	Day 1 AM Dose	_____ ___/___/___	Study Drug administered in clinic ____:____		
	Day 2 AM Dose	_____ ___/___/___	____:____		
	Day 3 AM Dose	_____ ___/___/___	____:____		
	Day 4 AM Dose	_____ ___/___/___	____:____		
	Day 5 AM Dose	_____ ___/___/___	____:____		
	Day 6 AM Dose	_____ ___/___/___	____:____		
	Day 7 AM Dose	_____ ___/___/___	____:____		
Week 1	Day 8 AM Dose	_____ ___/___/___	____:____		
	Day 9 AM Dose	_____ ___/___/___	____:____		
	Day 10 AM Dose	_____ ___/___/___	____:____		
	Day 11 AM Dose	_____ ___/___/___	____:____		
	Day 12 AM Dose	_____ ___/___/___	____:____		
	Day 13 AM Dose	_____ ___/___/___	____:____		
	Day 14 AM Dose	_____ ___/___/___	____:____		
	NOTE - *Do not take study drug tomorrow morning (Day 15). Bring study drug and diary to clinic visit.*				

16.3. Appendix III: Non-permitted and Permitted Medications

NON-PERMITTED MEDICATION AND CONDITION

Medications	**When**
Same pharmacological class (PPAR agonists)	
Thiazolidinediones (glitazones [pioglitazone and rosiglitazone])	From 3 months (12 weeks) prior to Screening Visit 1 up to end of study (EOS) Visit 7
Fibrates	From 2 months (8 weeks) prior to Screening (SV1) up to end of study (EOS) Visit 7
Medication that may induce steatosis/steatohepatitis	
Corticosteroids (parenteral & oral chronic administration)	No chronic use of more than 3 consecutive months permitted from 12 months prior to Screening (SV1) up to Randomization (Visit 1/Day 1).
Tamoxifen	
Methotrexate	
Tetracycline	
Valproic acid	
Salicylates	
Medication that may interact with absorption, metabolism, etc.	
Indomethacin	From Randomization (Visit 1/Day 1) up to EOT Visit 6

PERMITTED MEDICATION AND CONDITION

Medications	When
Antidiabetic therapy	
Insulin	No qualitative change (i.e., no initiation of a new drug) from at least 3 months prior Screening (SV1) Dose stability required from at least 3 months prior to Screening Visit 1 up to Randomization (Visit1/Day 1) From Randomization Visit 1 to EOS Visit 7, qualitative change and dose change should be avoided as much as possible
Metformin	
Gliptins	
Sulfonylureas	
GLP-1 agonists	
SGLT2- inhibitors	
Lipid lowering therapy	
Statins	Dose stability required from at least 3 months prior to Screening Visit up to Randomization (Visit 1/Day 1). From Randomization (Visit 1/Day 1) to EOS V7, qualitative change and dose change should be avoided as much as possible.
Ezetimibe	
Other nonfibrate lipid lowering therapies	
Medication that may induce steatosis/steatohepatitis	
Corticosteroids (parenteral & oral chronic administration)	From Randomization (Visit 1/Day 1) to EOS Visit 7, chronic use of more than 2 consecutive weeks should be avoided as much as possible.
Tamoxifen	
Methotrexate	
Tetracycline	
Valproic acid	
Salicylates	
Others	
Vitamin E	Dose stability required from at least 3 months prior to Screening Visit 1) up to Randomization (Visit 1/Day 1). From Randomization (Visit 1/day 1) to EOS Visit 7, qualitative change and dose change should be avoided as much as possible
PUFAs	
ursodeoxycholic acid	

GLP-1 =glucagon-like peptide 1; PUFA = polyunsaturated fatty acids; SGLT2 = sodium/glucose cotransporter 2.

16.4. Appendix IV: Clinical Trial Facilitation Group (CTFG) Highly Effective Methods of Birth Control

For the purpose of this guidance, methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods. Such methods include:

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[1]
  - oral
  - intravaginal
  - transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation[1]
  - oral
  - injectable
  - implantable[2]
- intrauterine device (IUD)[2]
- intrauterine hormone-releasing system (IUS)[2]
- bilateral tubal occlusion[2]
- vasectomised partner[2,3]
- sexual abstinence[4]

[1]Hormonal contraception may be susceptible to interaction with the investigational medicinal product (IMP), which may reduce the efficacy of the contraception method.

[2]Contraception methods that in the context of this guidance are considered to have low user dependency.

[3]Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the woman of childbearing potential (WOCBP) trial participant and that the vasectomised partner has received medical assessment of the surgical success.

[4] In the context of this guidance sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. 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 subject.

Source: Clinical Trial Facilitation Group (CTFG). Recommendations related to contraception and pregnancy testing in clinical trials. 2014, section 4, p. 9

16.5. Appendix V – List of Abbreviations

Abbreviation	Definition
A1AT	Alpha-1-antitrypsin
AAP	American Academy of Pediatrics
ADR	Adverse drug reaction
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AMA	Antimitochondrial Assay
ApoAI	Apolipoprotein A-I
ApoB	Apolipoprotein B
AST	Aspartate aminotransferase
AT	Aminotransferase
$AUC_{(0-24)}$	Area under the plasma concentration time curve over 24 hours
BMI	Body mass index
BP	Blood pressure
BPM	Beats per minute
CA	Competent Authorities
CFR	Code of Federal Regulations
CK	Creatine kinase
CPK	Creatinine phosphokinase
CI	Confidence interval
C_{max}	Maximum concentration observed
COA	Certificate of Analysis
COVID-19	Coronavirus disease of 2019
CRF	Case report form
CRO	Contract Research Organization
CTFG	Clinical Trial Facilitation Group
CV	Coefficient of Variation
DBP	Diastolic blood pressure
dL	Deciliter
DSMB	Data Safety and Monitoring Board
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
eGFR	Estimated glomerular filtration rate
EOS	End of Study
EOT	End of Treatment
ELISA	Enzyme-linked immunosorbent assay
EU	European Union
FDA	Food and Drug Administration
FFA	Fatty free acids
FOCBP	Females of childbearing potential
FPFV	First patient/first visit
GLP-1	Glucagon-like peptide 1
GCP	Good Clinical Practice
GGT	Gamma glutamyl transferase
HAV	Hepatitis A virus
HbA1c	Hemoglobin A1C
HBsAg	Hepatitis B surface antigen
hsCRP	High sensitivity C-reactive protein
HCV	Hepatitis C virus
HDL	High-density lipoprotein

Abbreviation	Definition
HDL-C	High-density lipoprotein cholesterol
HEV	Hepatitis E virus
HIV	Human immunodeficiency virus
HIPAA	Health Insurance Portability and Accountability Act
HOMA-IR	Homeostasis Model Assessment of Insulin Resistance
ICF or IC	Informed Consent Form
ICH	International Council on Harmonization
IEC	Independent Ethics Committee
IND	Investigational New Drug Application
INR	International normalized ration
IRB	Institutional Review Board
ITT	Intent to treat
IU	International Unit
L	Liter
LDL-C	Low-density lipoprotein cholesterol
LLNA	Local Lymph node assay
LOQ	Lower limit of assay
LPLV	Last patient last visit
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mg/dL	Milligram per deciliter
mL	Milliliter
mm	Millimeter
mmHg	Millimeter of mercury
MTD	Maximum tolerated dose
NAFL	Nonalcoholic fatty liver
NAFLD	Nonalcoholic fatty liver disease
NASH	Nonalcoholic steatohepatitis
NCA	Non compartmental analysis
PBC	Primary biliary cholangitis
PD	Pharmacodynamic
PedsQL™	Pediatric Quality of Life
PK	Pharmacokinetic(s)
PND	Post-natal day
PPAR	Peroxisome proliferator-activated receptor
PR	Pulse rate
PUFAs	Polyunsaturated fatty acids
RBC	Red blood cells
SADR	Serious adverse drug reaction
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SD	Standard deviation
SGLT2	Sodium/glucose cotransporter 2
SUSAR	Suspected unexpected serious adverse reaction
TC	Total cholesterol
T_{max}	Time to maximum concentration
TEAE	Treatment emergent adverse event
TIBC	Total iron binding capacity
TG	Triglycerides
TSH	Thyroid stimulation hormone
UA	Urinalysis
ULN	Upper limit of normal
UV	Ultraviolet
US	United States

Abbreviation	Definition
VLDL-C	Very low-density lipoprotein
WBC	White blood cells
WHO	World Health Organization
WHODD	World Health Organization Drug Dictionary
WMA	World Medical Association
WOCBP	Woman of childbearing potential

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