STATISTICAL ANALYSIS PLAN

Study Title:	A Proof of Concept, Open-Label Study Evaluating the Safety, Tolerability, and Efficacy of Regimens in Subjects with Nonalcoholic Steatohepatitis (NASH)
Name of Test Drug:	Selonsertib (SEL, GS-4997); GS-0976; GS-9674
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CONFIDENTIAL AND PROPRIETARY INFORMATION

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CCI [redacted]

LIST OF ABBREVIATIONS

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
APRI	AST to platelet ratio
AST	aspartate aminotransferase
BLQ	below the limit of quantitation
BMI	body mass index
CCI	[redacted]
CI	confidence interval
CLDQ	chronic liver disease questionnaire
CK	creatine kinase
CK-18	cytokeratin-18
CRP	C-reactive protein
CSR	clinical study report
CTCAE	Common Toxicity Criteria for Adverse Events
DILI	drug-induced liver injury
DMC	data monitoring committee
ECG	electrocardiogram
eCRF	electronic case report form
CCI	[redacted]
ET	early termination
FAS	Full Analysis Set
FIB-4	fibrosis-4
FU	follow-up
GGT	gamma-glutamyl transferase
HA	hyaluronic acid
HDL	high density lipoprotein
HDL-C	HDL-cholesterol
HLT	high-level term
CCI	[redacted]
ICH	International Conference on Harmonization (of Technical Requirements for Registration of Pharmaceuticals for Human Use)
IFG	impaired fasting glucose
INR	international normalization ratio
LDL-C	low density lipoprotein cholesterol
LTT	lower-level term
LOQ	limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
MELD	model for end-stage liver disease

MRE	magnetic resonance elastography
MRI-PDFF	magnetic resonance imaging – proton density fat fraction
NAFLD	non-alcoholic fatty liver disease
NFS	NAFLD fibrosis score
PIIINP	procollagen III amino terminal peptide
CCI	[redacted]
PT	preferred term
Q1, Q3	first quartile, third quartile
SAP	statistical analysis plan
SD	standard deviation
SF-36	Short Form (36) Health Survey
SI (units)	international system of units
SOC	system organ class
TEAE	treatment-emergent adverse event
TFLs	tables, figures, and listings
TIMP-1	tissue inhibitor of metalloproteinase
ULN	upper limit of normal
VLDL-C	very low density lipoprotein cholesterol
WHO	World Health Organization

PHARMACOKINETIC ABBREVIATIONS

AUC_{last}	area under the concentration versus time curve from time zero to the last quantifiable concentration
AUC_{tau}	area under the concentration versus time curve over the dosing interval
C_{last}	last observed quantifiable concentration of the drug
C_{max}	maximum observed concentration of drug
C_{tau}	observed drug concentration at the end of the dosing interval
CLss/F	apparent oral clearance after administration of the drug: at steady state: CLss/F = Dose/AUC_{tau} , where "Dose" is the dose of the drug
$t_{1/2}$	estimate of the terminal elimination half-life of the drug, calculated by dividing the natural log of 2 by the terminal elimination rate constant (λ_z)
T_{last}	time (observed time point) of C_{last}
T_{max}	time (observed time point) of C_{max}
λz	terminal elimination rate constant, estimated by linear regression of the terminal elimination phase of the concentration of drug versus time curve

1. INTRODUCTION

This statistical analysis plan (SAP) describes the statistical analysis methods and data presentations to be used in tables, figures, and listings (TFLs) in the administrative Week 12 interim analysis and the final analysis and clinical study report (CSR) for Study GS-US-384-3914, Cohorts 10 and 11. This SAP is based on study protocol amendment 11 dated 26 September 2018 and the electronic case report form (eCRF). This SAP is for the analyses of Cohorts 10 and 11, and includes Cohorts 10 and 11 data only. Any changes made after the finalization of the SAP will be documented in the CSR.

1.1. Study Objectives

The primary objective of this study is as follows:

- To evaluate the safety and tolerability of study drug(s) in subjects with NASH as assessed by magnetic resonance imaging - proton density fat fraction (MRI-PDFF) and magnetic resonance elastography (MRE).

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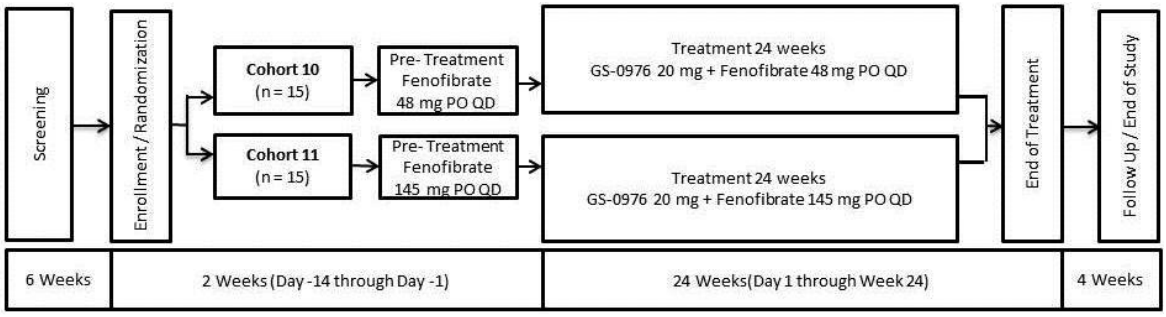
1.2. Study Design

This is a proof of concept, open-label study evaluating the safety, tolerability, and efficacy of monotherapy and combination regimens in subjects with NASH as assessed by MRI-PDFF and MRE.

For Cohorts 1 through 9, eligible subjects will be enrolled to receive treatment with selonsertib (SEL; GS-4997), GS-0976, GS-9674; the combination of SEL and GS-9674, SEL and GS-0976, GS-9674 and GS-0976; or SEL, GS-0976 and GS-9674 for 12 weeks. Data from Cohorts 1 through 9 will not be analyzed in the scope of this SAP. For the design and analysis of Cohorts 1 through 9, please refer to the SAP developed for Cohorts 1 to 9, dated 01 August 2018.

For Cohorts 10 and 11, eligible subjects will be randomized to receive pre-treatment with fenofibrate 48 mg or fenofibrate 145 mg from Day -14 to Day -1 and will be treated with GS-0976 20 mg and fenofibrate 48 mg or GS-0976 20 mg and fenofibrate 145 mg for 24 weeks as shown in the figure below. The data collected will be analyze separately by study phases as defined in Section 3.1, or for the entire study.



Approximately 30 subjects will be randomized (1:1) into either Cohort 10 or 11; randomization will be stratified by (1) Screening serum triglyceride levels ([≥ 150 mg/dL and < 250 mg/dL] or [≥ 250 mg/dL and < 500 mg/dL]), and (2) Fibrosis Stage (F3 defined by liver biopsy or Screening MRE with liver stiffness < 4.67 kPa, or F4 defined by liver biopsy or Screening MRE with liver stiffness ≥ 4.67 kPa). Approximately 60% of subjects in each Cohort should have cirrhosis (F4) based on Inclusion Criteria 5. Approximately 60% subjects in each cohort should have screening serum triglycerides ≥ 150 mg/dL and < 250 mg/dL as below:

- Cohort 10 (GS-0976 20 mg + Fenofibrate 48 mg) will consist of 15 subjects:

  Approximately 9 subjects with Screening serum triglycerides ≥ 150 mg/dL and < 250 mg/dL

  Approximately 6 subjects with Screening serum triglycerides ≥ 250 mg/dL and < 500 mg/dL

- Cohort 11 (GS-0976 20 mg + Fenofibrate 145 mg) will consist of 15 subjects:

  Approximately 9 subjects with Screening serum triglycerides ≥ 150 mg/dL and < 250 mg/dL

  Approximately 6 subjects with Screening serum triglycerides ≥ 250 mg/dL and < 500 mg/dL

1.3. Sample Size and Power

In Cohorts 10 and 11, it was assumed that among subjects with baseline hypertriglyceridemia ≥ 150 mg/dL (60% with serum triglycerides ≥ 150 and < 250 mg/dL and 40% with serum triglycerides ≥ 250 and < 500 mg/dL), Grade 3 to 4 hypertriglyceridemia (> 500 mg/dL) would be observed in 28% of subjects following treatment with GS-0976. Assuming that the co-administration of fenofibrate and GS-0976 will reduce the incidence of Grade 3 to 4 hypertriglyceridemia to < 5%, a sample size of 15 subjects in each of Cohorts 10 and 11 will provide 82% power to detect the reduction based on a one-sided exact test at a significance level of 0.05.

2. TYPE OF PLANNED ANALYSIS

This SAP is for the analyses of Cohorts 10 and 11 and includes Cohorts 10 and 11 data only. The interim analyses and final analyses discussed in this section are the interim analyses and final analyses of Cohorts 10 and 11, and will not involve Cohorts 1 to 9.

2.1. Interim Analyses

2.1.1. DMC Interim Analysis

There will be no formal DMC review for Cohorts 10 and 11. Therefore, no analyses will be conducted for the DMC.

2.1.2. Week 12 Interim Analysis

A Week 12 interim analysis will be conducted for administrative purposes after all subjects in Cohorts 10 and 11 complete Week 12 assessments or early discontinue study treatment. All safety and efficacy data from Cohorts 10 and 11 collected up to the time of interim analysis will be presented.

2.2. Final Analysis

After all subjects in Cohorts 10 and 11 have completed the study, outstanding data queries have been resolved or adjudicated as unresolvable, and the data have been cleaned and finalized, the final analysis of the data will be performed.

3. GENERAL CONSIDERATIONS FOR DATA ANALYSES

Analysis results will be presented using descriptive statistics. For categorical variables, the number and percentage of subjects in each category will be presented; for continuous variables, the number of subjects (n), mean, standard deviation (SD), median, first quartile (Q1), third quartile (Q3), minimum, and maximum will be presented.

By-subject listings will be presented for all subjects in the All Randomized Analysis Set and sorted by subject ID number, visit date, and time (if applicable). Data collected on log forms, such as AEs, will be presented in chronological order within the subject. The treatment group to which subjects were randomized will be used in the listings. Age, sex at birth, race, and ethnicity will be included in the listings, as space permits.

3.1. Study Phases

Study phases are defined according to the study drug(s) which subjects take during the study.

3.1.1. Pre-treatment Phase

Pre-treatment Phase is the phase when subjects were only taking fenofibrate study drug. It starts from the date of first dose of fenofibrate to the date before the first dose of GS-0976.

3.1.2. Treatment Phase

Treatment Phase is the phase when subjects were taking both GS-0976 and fenofibrate study drugs and through the follow-up visit. It starts from the date of first dose of GS-0976 to the end of study.

3.1.3. Entire Study

Entire Study is the combination of the Pre-treatment Phase and the Treatment Phase.

3.2. Analysis Sets

Analysis sets define the subjects to be included in an analysis. Analysis sets and their definitions are provided in this section. The analysis set will be identified and included as a subtitle of each table, figure, and listing.

For each analysis set, the number and percentage of subjects included will be summarized by treatment group. The denominator will be the number of subjects randomized in the corresponding treatment group. Subjects who have been randomized but never dosed will also be summarized. A listing of reasons for exclusion from analysis sets will be provided by subject.

3.2.1. All Randomized Analysis Set

All Randomized Analysis Set includes all subjects who were randomized into cohort 10 or 11of this study.

3.2.2. Full Analysis Set

The Full Analysis Set (FAS) includes all subjects who were randomized into cohort 10 or 11 and took at least 1 dose of GS-0976.

This is the primary analysis set for efficacy analyses.

3.2.3. Safety Analysis Set

The Safety Analysis Set includes all subjects who took at least 1 dose of GS-0976.

This is the primary analysis set for safety analyses.

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CCI [redacted]

3.2.6. Pre-treatment Safety Analysis Set

The Pre-treatment Safety Analysis Set includes all subjects who received at least 1 dose of fenofibrate in the Pre-treatment Phase.

This is the analysis set for Pre-treatment Phase safety analysis.

3.3. Subject Grouping

For analyses based on the FAS, subjects will be grouped according to the treatment to which they were randomized. For analyses based on the Safety Analysis Set, Pre-treatment Safety Analysis Set and CCI [redacted], subjects will be grouped according to the actual treatment

received. The actual treatment received will differ from the randomized treatment only when their actual treatment differs from randomized treatment for the entire treatment duration.

For safety analysis of the Pre-treatment Phase, subjects in the Pre-treatment Safety Analysis Set will be analyzed and will be grouped into the following:

1) Fenofibrate 48 mg PO QD

2) Fenofibrate 145 mg PO QD

For analysis of the Treatment Phase or the Entire Study, subjects in the Safety Analysis Set and CCI will be analyzed and will be grouped into the following:

3) GS-0976 20 mg + Fenofibrate 48 mg PO QD

4) GS-0976 20 mg + Fenofibrate 145 mg PO QD

3.4. Strata and Covariates

Subjects will be randomly assigned to treatment groups in a 1:1 ratio using a stratified randomization schedule. Stratification will be based on the following variables:

- Screening serum triglyceride levels ([≥ 150 mg/dL and < 250 mg/dL] or [≥ 250 mg/dL and < 500 mg/dL])
- Fibrosis stage ([F3 defined by liver biopsy or screening MRE with liver stiffness < 4.67 kPa] or [F4 defined by liver biopsy or screening MRE with liver stiffness ≥ 4.67 kPa])

3.5. Examination of Subject Subgroups

Subgrouping of subjects based on fibrosis stage at randomization and Pre-treatment baseline of Triglycerides will be explored for subgroup analyses. Selected efficacy endpoints as defined in Section 6.2.3 will be summarized by treatment group and further by the following subgroups within each treatment group.

- Pre-treatment baseline triglyceride level ([< 250 mg/dL] or [≥ 250 mg/dL])
- Fibrosis stage (F3 or F4)

3.6. Multiple Comparisons

Adjustments for multiplicity will not be made, because no formal statistical testing will be performed in this study.

3.7. Missing Data and Outliers

3.7.1. Missing Data

In general, missing data will not be imputed unless methods for handling missing data are specified. Exceptions are presented in this document.

For missing last dosing date of study drug, imputation rules are described in Section 4.2.1. The handling of missing or incomplete dates for AE onset is described in Section 7.1.5.2, and for prior and concomitant medications in Section 7.4.

3.7.2. Outliers

Outliers will be identified during the data management and data analysis process, but no sensitivity analyses will be conducted. All data will be included in the data analysis.

3.8. Data Handling Conventions and Transformations

The following conventions will be used for the imputation of date of birth when it is partially missing or not collected:

- If only month and year of birth is collected, then "15" will be imputed as the day of birth
- If only year of birth is collected, then "01 July" will be imputed as the day and month of birth
- If year of birth is missing, then date of birth will not be imputed

In general, age collected at Day 1 (in years) which is the date of first dose of study drug GS-0976 will be used for analyses and presented in listings. If age at Day 1 is not available for a subject, then age derived based on the date of birth and the Day 1 visit date will be used instead. If an enrolled subject was not dosed with GS-0976, the randomization date will be used instead of the Day 1 visit date. For screen failures, the date the first informed consent was signed will be used for the age derivation. Age required for longitudinal and temporal calculations and analyses (eg, estimates of creatinine clearance, age at date of AE) will be based on age derived from date of birth and the date of the measurement or event, unless otherwise specified.

Non-PK data that are continuous in nature but are less than the lower limit of quantitation (LOQ) or above the upper LOQ will be imputed as follows:

- A value that is 1 unit less than the lower LOQ will be used to calculate descriptive statistics if the datum is reported in the form of "< x" (where x is considered the lower LOQ). For example, if the values are reported as < 50 and < 5.0, values of 49 and 4.9, respectively, will be used to calculate summary statistics. An exception to this rule is any value reported as < 1 or < 0.1, etc. For values reported as < 1 or < 0.1, a value of 0.9 or 0.09, respectively, will be used to calculate summary statistics.

- A value that is 1 unit above the upper LOQ will be used to calculate descriptive statistics if the datum is reported in the form of "> x" (where x is considered the upper LOQ). Values with decimal points will follow the same logic as above.

- The LOQ will be used to calculate descriptive statistics if the datum is reported in the form of "≤ x" or "≥ x" (where x is considered the LOQ).

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3.9. Analysis Visit Windows

3.9.1. Definition of Study Day

3.9.1.1. Study Day in Pre-treatment Phase

Pre-treatment study day will be calculated from the first dosing date of fenofibrate and derived as follows:

- For postdose study days: Assessment Date First Dosing Date of Fenofibrate + 1
- For days prior to the first dose: Assessment Date First Dosing Date of Fenofibrate

Therefore, pre-treatment study day 1 is the day of first dose of fenofibrate administration.

3.9.1.2. Study Day in Treatment Phase

Study day will be calculated from the first dosing date of GS-0976 and derived as follows:

- For postdose study days: Assessment Date First Dosing Date of GS-0976 + 1
- For days prior to the first dose: Assessment Date First Dosing Date of GS-0976

Therefore, study day 1 is the day of first dose of GS-0976 administration.

3.9.2. Analysis Visit Windows

Subject visits might not occur on protocol-specified days. Therefore, for the purpose of analysis, observations will be assigned to analysis windows.

For the Treatment Phase, in general, the baseline value is defined as the last available value collected on or prior to the first dosing date of GS-0976. Baseline values for liver tests (ALT, AST, total bilirubin and direct bilirubin) will be determined by averaging the values obtained between and including Screening and Study Day 1. Selected safety and efficacy data collected up to and including the last dosing date plus 30 days will be mapped according to the analysis windows specified Section 3.9.2.2 unless the nominal visit name is Follow-Up (FU). Quality of life (QoL) assessments will use nominal baseline values.

For the Pre-treatment Phase and the Entire Study, the baseline value is defined as the last available value collected on or prior to the first dosing date of fenofibrate. Only selected safety analysis will be conducted for the Pre-treatment Phase and for the Entire Study. Selected safety lab data collected up to and including the first dosing date of GS-0976 will be mapped according to the analysis window specified in Section 3.9.2.1 and summarized for the Pre-treatment Phase. Selected safety lab data collected up to and including the last dosing date plus 30 days will be mapped according to the analysis window specified in Section 3.9.2.3 and summarized for the Entire Study.

The unscheduled visits and early termination (ET) visits will be windowed, but the follow-up (FU) visits will be summarized as a separate visit, and labeled "Follow-up Visit". Data obtained after the follow-up visit or last dose date plus 30 days (whichever is later) will be excluded from the summaries, but will be included in the listings.

3.9.2.1. Analysis Windows for Pre-treatment Phase

Data included in the pre-treament safety analysis will include data collected from screening and up to and including the first dosing date of GS-0976. The analysis windows for selected safety data as specified in Section 7.2.1.2 are provided in Table 3-1.

Table 3-1. Pre-treatment Phase Safety Analysis Visit Windows for Chemistry, Hematology, Coagulation Labs, CCI [redacted], and Free Fatty Acids

Analysis Visit	Nominal Pre-treatment Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Pre-treatment Baseline	1	(none)	1
Day -11	4	2	5
Day -7	8	6	11
Day 1	15	12	≥ 15 if didn't take GS-0976
			1st dosing date of GS-0976 if took GS-0976

3.9.2.2. Analysis Visit Window for Treatment Phase

The analysis windows for selected efficacy and safety data are provided in Table 3-2 and Table 3-3. CCI [redacted]

Table 3-2. Treatment Phase Analysis Visit Windows for Vital Signs, CCI Chemistry, Hematology, Coagulation Panel, CCI , Free Fatty Acids, CCI Glucose, Insulin, Bile Acids, Model for End-stage Liver Disease (MELD) Score, AST to Platelet Ratio Index (APRI), Fibrosis-4 (FIB-4), Non-alcoholic Fatty Liver Disease (NAFLD) Fibrosis Score (NFS), and Apolipoprotein A1

Analysis Visit	Nominal Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Baseline	1	(none)	1
Week 1	8	2	18
Week 4	29	19	42
Week 8	57	43	70
Week 12	85	71	98
Week 16	113	99	140
Week 24	169	141	≥ 169

* APRI, FIB 4 and NFS are defined in Appendix 3.

Table 3-3. Treatment Phase Analysis Visit Windows for MRI-PDFF, MRE, CCI Procollagen III Amino Terminal Peptide[PIIINP], Tissue Inhibitor of Metalloproteinase 1[TIMP-1]), CCI , Alpha-2 Macroglobin, Haptoglobin, CCI including liver stiffness and CCI C-Reactive Protein (CRP) , Hemoglobin A1c, Cytokeratin 18 (CK-18)

Analysis Visit	Nominal Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Baseline	1	(none)	1
Week 12	85	2	126
Week 24	169	127	≥ 169

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3.9.2.3. Analysis Windows for Entire Study

For the safety analysis of the Entire Study, no separate analysis windows will be created based on pre-treatment study day or study day. Instead, the mapped analysis visits in both phases will be renamed as in Table 3-4 for entire study safety analysis. The pre-treatment baseline is to be mapped to overall baseline.

Table 3-4. Entire Study Analysis Visit Rename for Chemistry, Hematology, Coagulation Labs, and CCI

Pre-treatment/Treatment Phase Analysis Visit	Entire Study Analysis Visit
Pre-treatment Baseline	Overall Baseline
Day -11	Overall Day 4
Day -7	Overall Week 1
Day 1	Overall Week 2
Week 1	Overall Week 3
Week 4	Overall Week 6
Week 8	Overall Week 10
Week 12	Overall Week 14
Week 16	Overall Week 18
Week 24	Overall Week 26

3.9.3. Selection of Data in the Event of Multiple Records in an Analysis Visit Window

Depending on the statistical analysis method, single values may be required for each analysis window. For example, change from baseline by visit usually requires a single value, whereas a time-to-event analysis would not require 1 value per analysis window.

If multiple valid, nonmissing, measurements exist in an analysis window, records will be chosen based on the following rules if a single value is needed:

- For baseline, the last nonmissing value on or prior to the first dosing date of study drug in the corresponding phase will be selected, unless specified differently. If there are multiple records with the same time or no time recorded on the same day, the baseline value will be the average of the measurements for continuous data, or the measurement with the lowest severity (eg, normal will be selected over abnormal for safety electrocardiogram [ECG] findings) for categorical data.

- Baseline values of the liver tests (ALT, AST, total bilirubin and direct bilirubin) in the treatment phase will be determined by averaging the values obtained from Screening to Study Day 1.

- For postbaseline values:

  The record closest to the nominal day for that visit will be selected.

  If there are 2 records that are equidistant from the nominal day, the later record will be selected.

  If there is more than 1 record on the selected day, the average will be taken for continuous data and the worse severity will be taken for categorical data, unless otherwise specified.

  For serum creatinine, if both enzymatic and regular creatinine are collected from the same blood sample and are analyzable, regular creatinine will be picked for analysis.

Liver stiffness by transient elastography data in each analysis visit window will be chosen based on the following rules:

- For baseline, measurements by XL probe will be selected for analysis if available, otherwise measurements by M probe will be selected.

- For postbaseline visits, measurements by the same probe type (XL or M) as baseline for the subject will be selected if available. If no measurement by the same probe type as baseline is available, the measurement by a different probe at postbaseline is then selected. If there are multiple records by the same probe type as baseline, the rules to choose postbaseline continuous measurements as described above will apply.

[redacted]

4. SUBJECT DISPOSITION

4.1. Subject Enrollment and Disposition

A summary of subject enrollment will be provided by treatment group and overall for each country and investigator within a country. The summary will present the number and percentage of subjects enrolled. For each column, the denominator for the percentage calculation will be the total number of subjects analyzed for that column.

The randomization schedule used for the study will be provided as an appendix to the CSR.

A summary of subject disposition will be provided by treatment group and study phase. This summary will present the number of subjects screened, the number of subjects who met all eligibility criteria but were not randomized with reasons subjects not randomized, the number of subjects randomized, and the number of subjects in each of the categories listed below :

- Pre-treatment Safety Analysis Set
- Completed pre-treatment study drug
- Did not complete pre-treatment study drug with reasons for premature discontinuation of pre-treatment study drug
- Safety Analysis Set
- Full Analysis Set
- [redacted]
- [redacted]
- Continuing study drug (for Week 12 Interim Analysis)
- Completed study drug
- Did not complete study drug with reasons for premature discontinuation of study drug
- Continuing study (for Week 12 Interim Analysis)
- Completed study
- Did not complete the study with reasons for premature discontinuation of study

For the status of study drug and study completion and reasons for premature discontinuation, the number and percentage of subjects in each category will be provided. The denominator for the

percentage calculation will be the total number of subjects in the All Randomized Analysis Set corresponding to that column. In addition, a flowchart will be provided to depict the disposition.

The following by-subject listings will be provided by subject identification (ID) number in ascending order to support the above summary tables:

- Reasons for premature study drug or study discontinuation
- Reasons for screen failure (will be provided by screening ID number in ascending order)
- Subjects with different triglycerides level between screening and pre-treatment baseline

4.2. Extent of Study Drug Exposure and Adherence

Extent of exposure to study drug will be examined by assessing the total duration of exposure to study drug and the level of adherence relative to the study drug regimen specified in the protocol.

4.2.1. Duration of Exposure to Study Drug

Duration of exposure to study drug will be summarized for the Pre-treatment Phase (fenofibrate only) by treatment group for the Pre-treatment Safety Analysis Set, and for the Entire Study (GS-0976 and fenofibrate) by treatment group for the Safety Analysis Set.

Total duration of exposure to fenofibrate in the Pre-treatment Phase will be defined as the last dosing date of fenofibrate in the pre-treatment phase or the date prior to the first dosing date of GS-0976, which is earlier, minus the first dosing date of fenofibrate plus 1 divided by 7, regardless of any temporary interruption in fenofibrate administration.

Total duration of exposure to study drug for the Entire Study will be summarized separately for fenofibrate and GS-0976, and will be defined as last dosing date of the corresponding study drug minus first dosing date of the corresponding study drug plus 1 divided by 7, regardless of any temporary interruptions in study drug administration.

Total duration of exposure will be expressed in weeks using up to 1 decimal place (eg, 4.5 weeks). If the last study drug dosing date is missing, the latest date among the study drug end date, clinical visit date, laboratory sample collection date, and vital signs assessment date that occurred during the on-treatment period will be used for subjects included in the final analyses or the last available date in the database snapshot for subjects who were still on treatment at the time of an interim analysis.

The total duration of exposure to study drug will be summarized using descriptive statistics and using the number (ie, cumulative counts) and percentage of subjects exposed through the following time periods in the Pre-treatment Phase: 1 day,1 week, 2 weeks, and the following time periods in the Treatment Phase: 1 day, 1 week, 4 weeks, 8 weeks, 12 weeks, 16 weeks, 20 weeks, and 24 weeks.

No formal statistical testing is planned.

4.2.2. Adherence to Study Drug

The total number of doses administered will be summarized using descriptive statistics.

The presumed total number of doses administered to a subject will be determined by the data collected on the drug accountability CRF using the following formula:

$$\text{Total Number of Doses Administered} \left(\sum \text{No. of Doses Dispensed}\right) \left(\sum \text{No. of Doses Returned}\right)$$

The level of prescribed adherence to the study drug regimen will be determined by the total amount of study drug administered relative to the total amount of study drug specified by the protocol for a subject who completes treatment in the study.

The level of prescribed adherence will be expressed as a percentage using the following formula:

$$\text{Prescribed Adherence (\%)} \left(\frac{\text{Total Amount of Study Drug Administered}}{\text{Total Amount of Study Drug Specified by Protocol}}\right) \text{x } 100$$

Note: if calculated adherence rate is greater than 100%, the result will be set to 100%.

For subjects who complete treatment, the number of fenofibrate doses expected to be administered is 182 and the number of GS-0976 doses expected to be administered is 168.

Descriptive statistics for the level of prescribed adherence with the number and percentage of subjects belonging to adherence categories ($< 75\%$, ≥ 75 to $< 90\%$, $\geq 90\%$) will be provided by treatment group for the Safety Analysis Set.

No formal statistical testing is planned.

A by-subject listing of study drug administration and drug accountability will be provided separately by subject ID number (in ascending order) and visit (in chronological order).

4.3. Protocol Deviations

Subjects who did not meet the eligibility criteria for study entry, but enrolled in the study will be summarized regardless of whether they were exempted by the sponsor or not. The summary will present the number and percentage of subjects who did not meet at least 1 eligibility criterion by treatment group based on the All Randomized Analysis Set. A by-subject listing will be provided for those subjects who did not meet at least 1 eligibility (inclusion or exclusion) criterion. The listing will present the eligibility criterion (or criteria if more than 1 deviation) that subjects did not meet and related comments, if collected.

Protocol deviations occurring after subjects entered the study are documented during routine monitoring. The number and percentage of subjects with important protocol deviations by deviation reason (eg, nonadherence to study drug, violation of select inclusion/exclusion criteria) will be summarized by treatment group for the All Randomized Analysis Set. A by-subject listing will be provided for those subjects with important protocol deviation.

5. BASELINE CHARACTERISTICS

5.1. Demographics

Subject demographic variables (ie, age, sex, race, and ethnicity) will be summarized by treatment group and overall using descriptive statistics for age, and using number and percentage of subjects for sex, race, and ethnicity. The summary of demographic data will be provided for the Safety Analysis Set. Age will be calculated in years at the date of first dosing date of GS-0976.

A by-subject demographic listing, including the informed consent date, will be provided by subject ID number in ascending order.

5.2. Other Baseline Characteristics

Other baseline characteristics will be summarized for the Treatment Phase only, which shows the baseline information before taking study drug GS-0976. These baseline characteristics include:

[redacted]

- Height (in cm)
- Body mass index (BMI; in kg/m^2)
- BMI category (< 18.5 kg/m^2, 18.5 to < 25 kg/m^2, 25 to 30 kg/m^2 and ≥ 30 kg/m^2)
- Screening fibrosis stage
- Screening triglyceride level category ([$\geq$ 150 mg/dL and $<$ 250 mg/dL] or [$\geq$ 250 mg/dL and $<$ 500 mg/dL])
- Pre-treatment triglyceride level ($<$ 250 mg/dL or $>$ 250mg/dL)
- Diabetes mellitus (absence or presence)
- Smoking status
- MRI-PDFF (%)
- MRE (kPa)
- Liver stiffness by transient elastography (kPa)
- Liver stiffness category (< 9.9 kPa, ≥ 9.9 to < 11.4 kPa, ≥ 11.4 kPa)

[redacted]

- [redacted]
- [redacted]
- APRI
- FIB-4
- NFS
- NFS category (< -1.455, -1.455 to < 0.676, and ≥ 0.676)
- MELD score
- CRP (mg/dL)
- CK-18 (M30 and M65) (for Final Analysis Only)
- Albumin (g/dL)
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- International normalized ratio (INR)
- [redacted]
- Fasting insulin (uIU/mL)
- Fasting glucose (mg/dL)
- Hemoglobin A1c (%)
- Total cholesterol (mg/dL)
- High density lipoprotein -cholesterol (HDL-C) (mg/dL)

[redacted]

[redacted]

- Calculated fasting non-HDL-C (total cholesterol minus HDL-C) (mg/dL)
- Calculated fasting very low density lipoprotein cholesterol (VLDL-C) (triglycerides divided by 5) (mg/dL)
- Calculated fasting low density lipoprotein cholesterol (LDL-C) (non-HDL-C minus VLDL-C) (mg/dL)
- Fasting total bile acids (umol/L)

These baseline characteristics will be summarized by treatment group and overall using descriptive statistics for continuous variables and using number and percentage of subjects for categorical variables. The summary of baseline characteristics will be provided for the Safety Analysis Set. No formal statistical testing is planned.

A by-subject listing of other baseline characteristics will be provided by subject ID number in ascending order.

5.3. Medical History

General medical history data will be collected at screening and listed only. General medical history data will not be coded.

A by-subject listing of general medical history will be provided by subject ID number in ascending order and abnormalities in chronological order.

[redacted]

[redacted]

[redacted]

CCI [redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

[redacted]

CCI [redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

CCI [redacted]

7. SAFETY ANALYSES

7.1. Adverse Events and Deaths

7.1.1. Adverse Event Dictionary

Clinical and laboratory adverse events (AEs) will be coded using the current version of MedDRA. System organ class (SOC), high-level group term (HLGT), high-level term (HLT), preferred term (PT), and lower-level term (LLT) will be provided in the AE dataset.

7.1.2. Adverse Event Severity

Adverse events are graded by the investigator as Grade 1, 2, 3, 4, or 5 according to toxicity criteria specified in the protocol. The severity grade of events for which the investigator did not record severity will be categorized as "missing" for tabular summaries and data listings. The missing category will be listed last in summary presentation.

Severity of adverse events will be determined by the investigator as mild, moderate, or severe. The severity of events for which the investigator did not record severity will be categorized as "missing" for tabular summaries and data listings. The missing category will be listed last in summary presentation.

7.1.3. Relationship of Adverse Events to Study Drug

Related AEs are those for which the investigator selected "Related" on the AE CRF to the question of "Related to Study Treatment." Relatedness will always default to the investigator's choice, not that of the medical monitor. Events for which the investigator did not record relationship to study drug will be considered related to study drug for summary purposes. However, by-subject data listings will show the relationship as missing.

7.1.4. Serious Adverse Events

Serious adverse events (SAEs) will be identified and captured as SAEs if the AEs met the definitions of SAEs that were specified in the study protocol. SAEs captured and stored in the clinical database will be reconciled with the SAE database from the Gilead Pharmacovigilence and Epidemiology Department before data finalization.

7.1.5. Treatment-Emergent Adverse Events

7.1.5.1. Definition of Treatment-Emergent Adverse Events

Treatment-emergent adverse events (TEAEs) for Cohorts 10 and 11 will be summarized separately for the Pre-treatment Phase and the Treatment Phase, as well as summarized for the Entire Study.

TEAEs in the Pre-treatment Phase are defined as 1 or both of the following:

- Any AEs with an onset date on or after the fenofibrate start date and no later than the date before the first dosing date of GS-0976
- Any AEs leading to premature discontinuation of fenofibrate in the Pre-treatment Phase.

TEAEs in the Treatment Phase are defined as 1 or both of the following:

- Any AEs with an onset date on or after the GS-0976 start date and no later than 30 days after permanent discontinuation of both study drugs
- Any AEs leading to premature discontinuation of any study drug in the Treatment Phase.

TEAEs in the Entire Study are defined as 1 or both of the following:

- Any AEs with an onset date on or after the fenofibrate start date and no later than 30 days after permanent discontinuation of both study drugs
- Any AEs leading to premature discontinuation of any study drug.

7.1.5.2. Incomplete Dates

If the onset date of the AE is incomplete and the AE stop date is not prior to the first dosing date of fenofibrate, then the month and year (or year alone if month is not recorded) of onset determine whether an AE is treatment emergent.

The event is considered treatment emergent for the Pre-treatment Phase if both of the following 2 criteria are met:

- The AE onset is the same as or after the month and year (or year) of the first dosing date of fenofibrate, and
- The AE onset date is the same as or before the month and year (or year) of the date prior to the first dosing date of GS-0976

The event is considered treatment emergent for the Treatment Phase if both of the following 2 criteria are met:

- The AE onset is the same as or after the month and year (or year) of the first dosing date of GS-0976, and
- The AE onset date is the same as or before the month and year (or year) of the date corresponding to 30 days after the date of the last dose of both study drugs

The event is considered treatment emergent for the Entire Study if both of the following 2 criteria are met:

- The AE onset is the same as or after the month and year (or year) of the first dosing date of fenofibrate, and
- The AE onset date is the same as or before the month and year (or year) of the date corresponding to 30 days after the date of the last dose of both study drugs

An AE with completely missing onset and stop dates will be considered treatment emergent in all phases. An AE with the onset date missing and a stop date later than the first dosing date of fenofibrate, will be considered to be treatment emergent in the Pre-treatment Phase and in Entire Study; moreover, if the stop date is later than the first dosing date of GS-0976, it will also be considered to be treatment emergent for the Treatment Phase. In addition, an AE with the onset date missing and incomplete stop date with the same or later month and year (or year alone if month is not recorded) as the first dosing date of fenofibrate will be considered treatment emergent in the Pre-treatment Phase and in Entire Study; moreover, if the incomplete stop date is with the same or later month and year (or year alone if month is not recorded) as the first dosing date of GS-0976, it will also be considered treatment emergent in the Treatment Phase.

7.1.6. Summaries of Adverse Events and Deaths

7.1.6.1. Summaries of Adverse Events and Deaths in The Treatment Phase

Treatment-emergent AEs in the treatment phase will be summarized based on the Safety Analysis Set.

A brief, high-level summary of the number and percentage of subjects who experienced at least 1 TEAEs during the Treatment Phase in the categories described below will be provided by treatment group. All deaths observed in the Treatment Phase will also be included in this summary.

The number and percentage of subjects who experienced at least 1 TEAE during the Treatment Phase will be provided and summarized by SOC, HLT (if applicable), PT, and treatment group. For other AEs described below, summaries will be provided by SOC, PT, and treatment group:

- TEAEs by severity grade
- TEAEs with Grade 3 or higher
- TEAEs with Grade 2 or higher
- TE treatment-related AEs
- All TE treatment-related AEs by severity grade

- TE treatment-related AEs with Grade 3 or higher
- TE treatment-related AEs with Grade 2 or higher
- TE SAEs
- TE treatment-related SAEs
- TEAEs leading to premature discontinuation of any study drug
- TEAEs leading to premature discontinuation of study
- TEAEs leading to dose modification or temporary interruption of any study drug
- TEAEs leading to death (ie, outcome of death)

Multiple events will be counted only once per subject in each summary. Adverse events will be summarized and listed first in alphabetic order of SOC (and HLT within each SOC if applicable), and then by PT in descending order of total frequency within each SOC. For summaries by severity grade, the most severe grade will be used for those AEs that occurred more than once in an individual subject during the study.

In addition to the above summary tables, the following tables will be summarized by PT only, in descending order of total frequency:

- All TEAEs
- TEAEs with Grade 3 or higher
- TEAEs with Grade 2 or higher
- TE treatment-related AEs
- TE treatment-related AEs with Grade 3 or higher
- TE treatment-related AEs with Grade 2 or higher
- TE SAEs
- TE treatment-related SAEs

7.1.6.2. Summaries of Adverse Events and Deaths in The Pre-Treatment Phase

Treatment-emergent AEs in the Pre-treatment Phase will be summarized based on the Pre-treatment Safety Analysis Set.

A brief, high-level summary of AEs as generated for the treatment phase will be provided for the Pre-treatment Phase AEs by treatment group and by the number and percentage of subjects who experienced the above AEs. All deaths observed in the study will also be included in this summary.

In addition to the above summary tables, the following tables will be summarized by PT only for Pre-treatment Phase AEs, in descending order of total frequency:

- TEAEs with Grade 3 or higher
- TE treatment-related AEs with Grade 3 or higher
- TE SAEs
- TE treatment-related SAEs

7.1.6.3. Summaries of Adverse Events and Deaths in The Entire Study

Treatment-emergent AEs in the Entire Study will be summarized based on the Safety Analysis Set.

The same set of summaries generated for Pre-treatment Phase AEs will be generated for the entire study AEs.

In addition, data listings for AEs in the Entire Study will be provided for the following:

- All AEs, indicating whether the event is treatment emergent in each study phase
- All AEs with severity of Grade 3 or higher
- SAEs
- All Deaths
- All AEs leading to premature discontinuation of study drug
- All AEs leading to dose modifications or temporary interruption of study drug

7.2. Laboratory Evaluations

Laboratory data collected during the study will be analyzed and summarized using both quantitative and qualitative methods. Summaries of laboratory data will be provided for the Pre-treatment Safety Analysis Set for the Pre-treatment Phase analysis and will include data collected up to the first dosing date of GS-0976. Summaries of laboratory data will also be provided for the Safety Analysis Set for the Treatment Phase analysis and Entire Study analysis, and will include data collected up to the last dose of both study drugs plus 30 days for subjects who have permanently discontinued study drug, or all available data at the time of the database snapshot

for subjects who were ongoing at the time of an interim analysis. The analysis will be based on values reported in conventional units. When values are below the LOQ, they will be listed as such, and the closest imputed value will be used for the purpose of calculating summary statistics as specified in Section 3.7. Hemolized test results will not be included in the analysis, but they will be listed in by-subject laboratory listings.

A by-subject listing for laboratory test results will be provided by subject ID number and visit in chronological order for hematology, serum chemistry, and coagulation separately for the Entire Study. Values falling outside of the relevant reference range and/or having a severity grade of 1 or higher on CTCAE version 4.03 severity grade will be flagged in the data listings, as appropriate.

No formal statistical testing is planned.

7.2.1. Summaries of Numeric Laboratory Results

7.2.1.1. Summaries of Numeric Laboratory Results in the Treatment Phase

CCI [redacted], albumin, glucose, insulin, CCI [redacted] hemoglobin A1c, and INR in the Treatment Phase will be summarized as efficacy endpoints and will not be repeated here. Descriptive statistics will be provided by treatment group for creatinine, estimated glomerular filtration rate (eGFR) using the Cockcroft-Gault equation, creatine kinase, white blood cells, neutrophils, lymphocytes, hemoglobin, platelets, and fasting free fatty acids will be summarized for the treatment phase as follows:

- Baseline values
- Values at each postbaseline visit
- Change from baseline at each postbaseline visit

A baseline laboratory value will be defined as the last measurement obtained on or prior to the date of first dose of GS-0976. Change from baseline to a postbaseline visit will be defined as the visit value minus the baseline value. The mean, median, Q1, Q3, minimum, and maximum values will be displayed to the reported number of digits; SD values will be displayed to the reported number of digits plus 1.

In the case of multiple values in an analysis window, data will be selected for analysis as described in Section 3.9.3.

7.2.1.2. Summaries of Numeric Laboratory Results in the Pre-Treatment Phase and in the Entire Study

Descriptive statistics will be provided by treatment group for the CCI [redacted], fasting free fatty acids, CCI [redacted], albumin, creatinine, eGFR, and creatine kinase for the pre-treatment phase and for entire study.

A baseline laboratory value for these two periods will be defined as the last measurement obtained on or prior to the date of first dose of fenofibrate, and referred to as the pre-treatment baseline. Change from pre-treatment baseline to visits afterwards will be summarized in the same way as in the treatment phase. Multiple values in an analysis window will be handled as in Section 3.9.3.

For the Pre-treatment Phase, the following visits will be presented besides pre-treatment baseline: Day -11, Day -7, and Day 1.

For the Entire Study, the following visits will be presented besides pre-treatment baseline: Day -11, Day -7, Day 1, Week 1, 4, 8, 12, 16, 24, and follow-up (FU).

7.2.2. Graded Laboratory Values

The CTCAE Version 4.03 will be used to assign toxicity grades (0 to 4) to laboratory results for analysis. Grade 0 includes all values that do not meet the criteria for an abnormality of at least Grade 1. For laboratory tests with criteria for both increased and decreased levels, analyses for each direction (ie, increased, decreased) will be presented separately.

For the baseline ALT, AST, total bilirubin and direct bilirubin in the treatment phase, the CTCAE version 4.03 will be used to assign toxicity grades to the derived average values. The reference range for each parameter will be defined as the one associated with the latest visit among all the values being averaged for each subject, for the purpose of determination of the abnormality and/or toxicity grades.

7.2.2.1. Treatment-Emergent Laboratory Abnormalities

7.2.2.1.1. Treatment-Emergent Laboratory Abnormalities in the Treatment Phase

Treatment-emergent laboratory abnormalities in the Treatment Phase are defined as values that increase at least 1 toxicity grade from baseline at any postbaseline time point, up to and including the date of last dose of both study drug plus 30 days for subjects who permanently discontinued study drug, or the last available date in the database snapshot for subjects who were still on treatment at the time of an interim analysis. If the relevant baseline laboratory value is missing, any abnormality of at least Grade 1 observed within the time frame specified above for the Treatment Phase will be considered treatment emergent.

7.2.2.1.2. Treatment-Emergent Laboratory Abnormalities in the Pre-Treatment Phase

Treatment-emergent laboratory abnormalities in the Pre-treatment Phase are defined as values that increase at least 1 toxicity grade from pre-treatment baseline at any post pre-treatment baseline time point, up to and including the date of first dose of GS-0976. If the relevant pre-treatment baseline laboratory value is missing, any abnormality of at least Grade 1 observed within the time frame specified above for the Pre-treatment Phase will be considered treatment emergent.

7.2.2.1.3. Treatment-Emergent Laboratory Abnormalities in the Entire Study

Treatment-emergent laboratory abnormalities in the Entire Study are defined as values that increase at least 1 toxicity grade from pre-treatment baseline at any post pre-treatment baseline time point, up to and including the date of last dose of both study drug plus 30 days for subjects who permanently discontinued study drug, or the last available date in the database snapshot for subjects who were still on treatment at the time of an interim analysis. If the relevant baseline laboratory value is missing, any abnormality of at least Grade 1 observed within the time frame specified for the Entire Study above will be considered treatment emergent.

7.2.2.2. Treatment-Emergent Marked Laboratory Abnormalities

7.2.2.2.1. Treatment-Emergent Marked Laboratory Abnormalities in the Treatment Phase

Treatment-emergent marked laboratory abnormalities in the Treatment Phase are defined as values that increase from baseline by at least 3 toxicity grades at any postbaseline time point, up to and including the date of the last dose of both study drug plus 30 days for subjects who permanently discontinued study drug or the last available date in the database snapshot for subjects who were still on treatment at the time of an interim analysis. If the relevant baseline laboratory value is missing, any Grade 3 or 4 values observed within the timeframe specified above for the Treatment Phase will be considered treatment-emergent marked abnormalities.

7.2.2.2.2. Treatment-Emergent Marked Laboratory Abnormalities in the Pre-Treatment Phase

Treatment-emergent marked laboratory abnormalities in the Pre-treatment Phase are defined as values that increase at least 3 toxicity grade from pre-treatment baseline at any post pre-treatment baseline time point up to and including the date of first dose of GS-0976. If the relevant pre-treatment baseline laboratory value is missing, any Grade 3 or 4 values observed within the time frame specified above for the Pre-treatment Phase will be considered treatment emergent.

7.2.2.2.3. Treatment-Emergent Laboratory Abnormalities in the Entire Study

Treatment-emergent laboratory marked abnormalities in the Entire Study are defined as values that increase at least 3 toxicity grade from pre-treatment baseline at any post pre-treatment baseline time point, up to and including the date of last dose of both study drug plus 30 days for subjects who permanently discontinued study drug, or the last available date in the database snapshot for subjects who were still on treatment at the time of an interim analysis. If the relevant baseline laboratory value is missing, any Grade 3 or 4 values observed within the time frame specified above for the Entire Study will be considered treatment emergent.

7.2.2.3. Summaries of Laboratory Abnormalities

Laboratory data that are categorical will be summarized using the number and percentage of subjects in the study with the given response at baseline and each scheduled postbaseline visit for the Treatment Phase, and will be summarized using the number and percentage of subjects in the

study with the given response at pre-treatment baseline and each scheduled post pre-treatment baseline visit for the Pre-Treatment Phase and the Entire Study.

The following summaries (number and percentage of subjects) for treatment-emergent laboratory abnormalities will be provided by lab test and treatment group; subjects will be categorized according to the most severe postbaseline abnormality grade for the Treatment Phase and the most severe post pre-treatment baseline abnormality grade for the Pre-treatment Phase and the Entire Study, for a given lab test:

- Graded laboratory abnormalities
- Grade 3 or 4 laboratory abnormalities
- Marked laboratory abnormalities

For all summaries of laboratory abnormalities, the denominator is the number of subjects with nonmissing postbaseline values for the Treatment Phase, and with nonmissing post pre-treatment baseline values for the Pre-treatment Phase and the Entire Study.

A by-subject listing of treatment-emergent Grade 3 or 4 laboratory abnormalities will be provided by subject ID number and visit in chronological order. This listing will include all test results that were collected throughout the study for the lab test of interest, with all applicable severity grades displayed.

7.2.3. Liver-related Laboratory Evaluations

Liver-related laboratory results will be summarized for the Treatment Phase only.

The summary will be provided by 2 subgroups of subjects according to their baseline CCI level in the treatment phase:

- Normal
- Elevated (> ULN)

Liver-related abnormalities after initial GS-0976 dosing will be examined and summarized using the number and percentage of subjects who were reported to have the following laboratory test values for postbaseline measurements:

For subjects with normal baseline CCI :

- Subjects meeting criteria for close observation

  CCI > 3 × ULN

- Subjects meeting criteria for study drug withheld

  CCI > 8 × ULN

  CCI > 5 × ULN for 2 weeks

  CCI > 3 × ULN and total bilirubin > 2 × ULN (or direct bilirubin > 2 × baseline in subjects with Gilbert's syndrome)

  CCI > 3 × ULN and INR > 1.5 (if not on anticoagulation)

For subjects with baseline CCI > ULN

- Subjects meeting criteria for close observation

  CCI > 2 × Baseline or > 300 U/L

- Subjects meeting criteria for study drug withheld

  CCI > 8 × Baseline or > 500 U/L

  CCI > 3 × Baseline or > 300 U/L, and total bilirubin > 2 × ULN (or direct bilirubin > 2 x Baseline in subjects with Gilbert's syndrome)

  CCI > 3 × Baseline and INR > 1.5 (if not on anticoagulation)

The above summary will include data from all postbaseline visits up to 30 days after the last dose of both study drug for subjects who permanently discontinued study drug, or the last available date in the database snapshot for subjects who were still on treatment at the time of an interim analysis. The denominator is the number of subjects in the Safety Analysis Set who have nonmissing postbaseline values of all relevant tests at the same postbaseline visit date in the summarizing group. A listing of subjects meeting any of the criteria above will be provided.

7.2.4. Additional Summary of Laboratory Value

Fasting triglycerides measured during the Pre-treatment Phase and at Day 1 will be summarized by treatment group by visit and further subgrouped by pre-treatment baseline triglycerides level ([≥ 150 mg/dL and < 250 mg/dL] or [≥ 250 mg/dL and < 500 mg/dL]), for the Pre-treatment Safety Analysis Group. The following by-visit summary will be reported.

- Pre-treatment baseline values
- Values at each post pre-treatment baseline visit
- Change from baseline at each post pre-treatment baseline visit

Fasting triglycerides grade measured during the Pre-treatment Phase and at Day 1 will be summarized using the number and percentage of subjects at each toxicity grade by treatment group by visit, for the Pre-treatment Safety Analysis Set. A similar summary further subgrouped by pre-treatment baseline triglyceride level will also be generated.

7.3. Vital Signs

Descriptive statistics will be provided by treatment group for vital signs in the Treatment Phase as follows:

- Baseline value
- Values at each postbaseline visit
- Change from baseline at each postbaseline visit

A baseline value will be defined as the last available value collected on or prior to the date/time of first dose of GS-0976. Change from baseline to a postbaseline visit will be defined as the postbaseline value minus the baseline value. Vital signs measured at unscheduled visits will be included for the baseline value selection.

In the case of multiple values in an analysis window, data will be selected for analysis as described in Section 3.9.3. No formal statistical testing is planned.

A by-subject listing of vital signs will be provided by subject ID number and visit in chronological order.

7.4. Prior and Concomitant Medications

Medications collected at screening and during the study will be coded using the current version of the World Health Organization (WHO) Drug dictionary.

7.4.1. Prior Medications

Prior medications are defined as any medications taken before a subject took the first dose of fenofibrate.

Prior medications will be summarized by preferred name using the number and percentage of subjects for each treatment group and overall. A subject reporting the same medication more than once will be counted only once when calculating the number and percentage of subjects who received that medication. The summary will be ordered by preferred term in order of descending overall frequency. For drugs with the same frequency, sorting will be done alphabetically.

For the purposes of analysis, any medication with a start date prior to the first dosing date of fenofibrate will be included in the prior medication summary regardless of when the stop date is. If a partial start date is entered the medication will be considered prior unless the month and year

(if day is missing) or year (if day and month are missing) of the start date are after the first dosing date of fenofibrate. Medications with a completely missing start date will be included in the prior medication summary, unless otherwise specified.

Summaries will be based on the Pre-Treatment Safety Analysis Set. No formal statistical testing is planned.

7.4.2. Concomitant Medications

Concomitant medications are defined as medications taken while a subject took study drug. Concomitant medications will be summarized separately for the Pre-treatment Phase based on the Pre-treatment Safety Analysis Set and for the Treatment Phase based on the Safety Analysis Set. Use of concomitant medications will be summarized by preferred name using the number and percentage of subjects for each treatment group. A subject reporting the same medication more than once will be counted only once when calculating the number and percentage of subjects who received that medication. The summary will be ordered by preferred term in descending overall frequency. For drugs with the same frequency, sorting will be done alphabetically.

For the purposes of analysis, any medications with a start date prior to or on the first dosing date of fenofibrate and continued to be taken after the first fenofibrate dosing date, or started after the first fenofibrate dosing date but prior to the first dosing date of GS-0976 will be considered concomitant medications in the Pre-Treatment Phase. Any medication with a start date prior to or on the first dosing date of GS-0976 and continued to be taken after the first GS-0976 dosing date, or started after the first GS-0976 dosing date but prior to the last dosing date of GS-0976 will be considered concomitant medication in the Treatment Phase. Medications started and stopped on the same day as the first dosing date or the last dosing date of fenofibrate/GS-0976 will also be considered concomitant in the Pre-treatment/Treatment Phase. Medications with a stop date prior to the date of first dosing date of fenofibrate or a start date after the first dosing date of GS-0976 will be excluded from the concomitant medication summary for the Pre-treatment Phase. Medications with a stop date prior to the date of the first dosing date of GS-0976 or a start date after the last dosing date of GS-0976 will be excluded from the concomitant medication summary for the Treatment Phase. If a partial stop date is entered, any medication with the month and year (if day is missing) or year (if day and month are missing) prior to the date of first study drug administration in the corresponding phase will be excluded from the concomitant medication summary for that phase. If a partial start date is entered, any medication with the month and year (if day is missing) or year (if day and month are missing) after the GS-0976 start date will be excluded from the concomitant medication summary for the Pre-treatment Phase, and any medication with the month and year (if day is missing) or year (if day and month are missing) after the GS-0976 stop date will be excluded from the concomitant medication summary for the Treatment Phase. Medications with completely missing start and stop dates will be included in the concomitant medication summary in both phases, unless otherwise specified. No formal statistical testing is planned.

All prior and concomitant medications (other than per-protocol study drugs) will be provided in a by-subject listing sorted by subject ID number and administration date in chronological order.

7.5. Electrocardiogram Results

7.5.1. Investigator Electrocardiogram Assessment

A by-subject listing for ECG assessment results will be provided by subject ID number and visit in chronological order.

7.6. Other Safety Measures

No additional safety measures are specified in the protocol.

7.7. Changes From Protocol-Specified Safety Analyses

There are no deviations from the protocol-specified safety analyses.

[redacted]

CCI [redacted]

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

CCI [redacted]

9. REFERENCES

Clopper CJ, Pearson ES. The Use of Confidence or Fiducial Limits Illustrated in the Case of the Binomial. Biometrika 1934;26 (4):404-13.

10. SOFTWARE

SAS® Software Version 9.4. SAS Institute Inc., Cary, NC, USA.

nQuery Advisor(R) Version X.0. Statistical Solutions, Cork, Ireland.

11. SAP REVISION

Revision Date (DD MMM YYYY)	Section	Summary of Revision	Reason for Revision

12. APPENDICES

Appendix 1. Schedule of Assessment for GS-US-384-3914 Cohorts 10 and 11
Appendix 2. CTCTAE Grade for Laboratory Parameters
Appendix 3. Noninvasive markers for Fibrosis
Appendix 4. Liver Function Prognostic Scores
Appendix 5. Health Related Quality of Life Score Calculation

Appendix 1. Schedule of Assessment for GS-US-384-3914 Cohorts 10 and 11

		Pretreatment Period			Enrollment	Treatment Period													EOT	ET	FU
		Kinetic Biomarkers Cycle 1							Kinetic Biomarker Cycle 2						Kinetic Biomarker Cycle 3						
	Screen[a]	D -14	D -11 (±1d)	D -7 (±1d)	D1[b]	D7 (W1) (±3d)	D28 (W4) (±3d)	D56 (W8) (±3d)	D70 (W10) (±1d)	D73 (±1d)	D77 (W11) (±3d)	D84 (W12) (±3d)	D112 (W16) (±3d)	D126 (W18) (±3d)	D154 (W22) (±1d)	D157 (±1d)	D161 (W23) (±1d)	D168 (W24) (±3d)	ET	D196 (W28) (±5d)
Clinical Assessment																				
Informed Consent	X																			
Determine Eligibility[c]	X	X			X															
Medical History	X	X			X															
Assess ascites and hepatic encephalopathy	X				X	X	X	X				X	X					X	X	
CPT score	X				X	X	X	X				X	X					X	X	
Physical Examination	X	X[d]			X[d]	X[d]	X[d]	X[d]				X[d]	X[d]					X[d]	X	X[d]
Vital Signs	X	X			X	X	X	X				X	X					X	X	X
Height	X																			
CCI																				
12 lead ECG	X											X						X	X	
QoLs[e]					X							X						X	X	
CCI																				
MRE, MRI PDFF	X[g]											X						X	X	
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense fenofibrate		X						X						X						

		Pretreatment Period			Enrollment	Treatment Period													EOT	ET	FU
		Kinetic Biomarkers Cycle 1							Kinetic Biomarker Cycle 2						Kinetic Biomarker Cycle 3						
	Screen[a]	D -14	D -11 (±1d)	D -7 (±1d)	D1[b]	D7 (W1) (±3d)	D28 (W4) (±3d)	D56 (W8) (±3d)	D70 (W10) (±1d)	D73 (±1d)	D77 (W11) (±3d)	D84 (W12) (±3d)	D112 (W16) (±3d)	D126 (W18) (±3d)	D154 (W22) (±1d)	D157 (±1d)	D161 (W23) (±1d)	D168 (W24) (±3d)	ET	D196 (W28) (±5d)
Dispense GS 0976					X		X	X				X	X	X						
Dispense Deuterated Water		X[k]							X						X					
Laboratory Assessments																				
Chemistry	X	X	X	X	X	X	X	X				X	X					X	X	X
Hematology	X	X	X	X	X	X	X	X				X	X					X	X	X
Coagulation Panel	X	X	X	X	X	X	X	X				X	X					X	X	X
Pregnancy Test[h]	X				X		X	X				X	X		X			X	X	X
Adiponectin, beta hydroxybutyrate		X			X							X						X	X	
hsCRP		X			X							X						X	X	
ApoA1, ApoB, CCI NMR Lipoprofile		X			X	X	X	X				X	X					X	X	
CCI																				
Lipidomics		X			X	X	X	X				X	X					X		
CCI																				
FGF19, C4		X			X							X						X		
CCI																				

		Pretreatment Period			Enrollment	Treatment Period												EOT	ET	FU
		Kinetic Biomarkers Cycle 1							Kinetic Biomarker Cycle 2						Kinetic Biomarker Cycle 3					
	Screen[a]	D -14	D -11 (±1d)	D -7 (±1d)	D1[b]	D7 (W1) (±3d)	D28 (W4) (±3d)	D56 (W8) (±3d)	D70 (W10) (±1d)	D73 (±1d)	D77 (W11) (±3d)	D84 (W12) (±3d)	D112 (W16) (±3d)	D126 (W18) (±3d)	D154 (W22) (±1d)	D157 (±1d)	D161 (W23) (±1d)	D168 (W24) (±3d)	ET	D196 (W28) (±5d)
Hemoglobin A1c	X	X			X							X						X	X	
Urine Drug Screening	X																			
HIV 1, HBV & HCV Serology	X																			
CCI																				
CCI																				
Genomic Sample[j]					X															
CCI																				
Urine Collection for Kinetic Biomarkers		X	X	X	X	X[m]		X[m]	X	X	X	X		X	X	X	X	X	X	
Blood Collection for Kinetic Biomarkers		X	X	X	X	X[m]		X[m]	X	X	X	X		X	X	X	X	X	X	
CCI																				

a Screening assessments to be completed within 6 weeks prior to Day 14 visit. The screening period also may be extended under special circumstances with the explicit approval of Gilead Sciences.
b Day 1 assessments must be performed prior to dosing.
c Includes Review of historical liver biopsy obtained within the last 6 months of Screening (date of initial informed consent) for subjects with bridging fibrosis (F3) and within the last 12 months for subjects with cirrhosis (F4), to assess subject eligibility
d Symptom driven physical examination.
e For subjects with Quality of Life questionnaires available at Day 1.

[redacted]
g Screening [redacted], MRI PDFF, and MRE must be performed as baseline assessments regardless of presence of historical liver biopsy.
h Females of childbearing potential only: Serum pregnancy testing at screening, urine pregnancy testing will occur at Day 1 and every 4 weeks during the dosing period and for 30 days following the last dose of study drug.
[redacted]
j Genomic Sample collected for subjects who have not opted out of sample collection. No additional blood will be drawn.
k The first dose of 50 mL deuterated water will be administered under the supervision of investigative site personnel and monitored for at least 30 minutes after for any side effects.
[redacted]
m Predose Kinetic Biomarkers and 2 hour (± 1 hour) postdose Kinetic Biomarker

Appendix 2. CTCTAE Grade for Laboratory Parameters

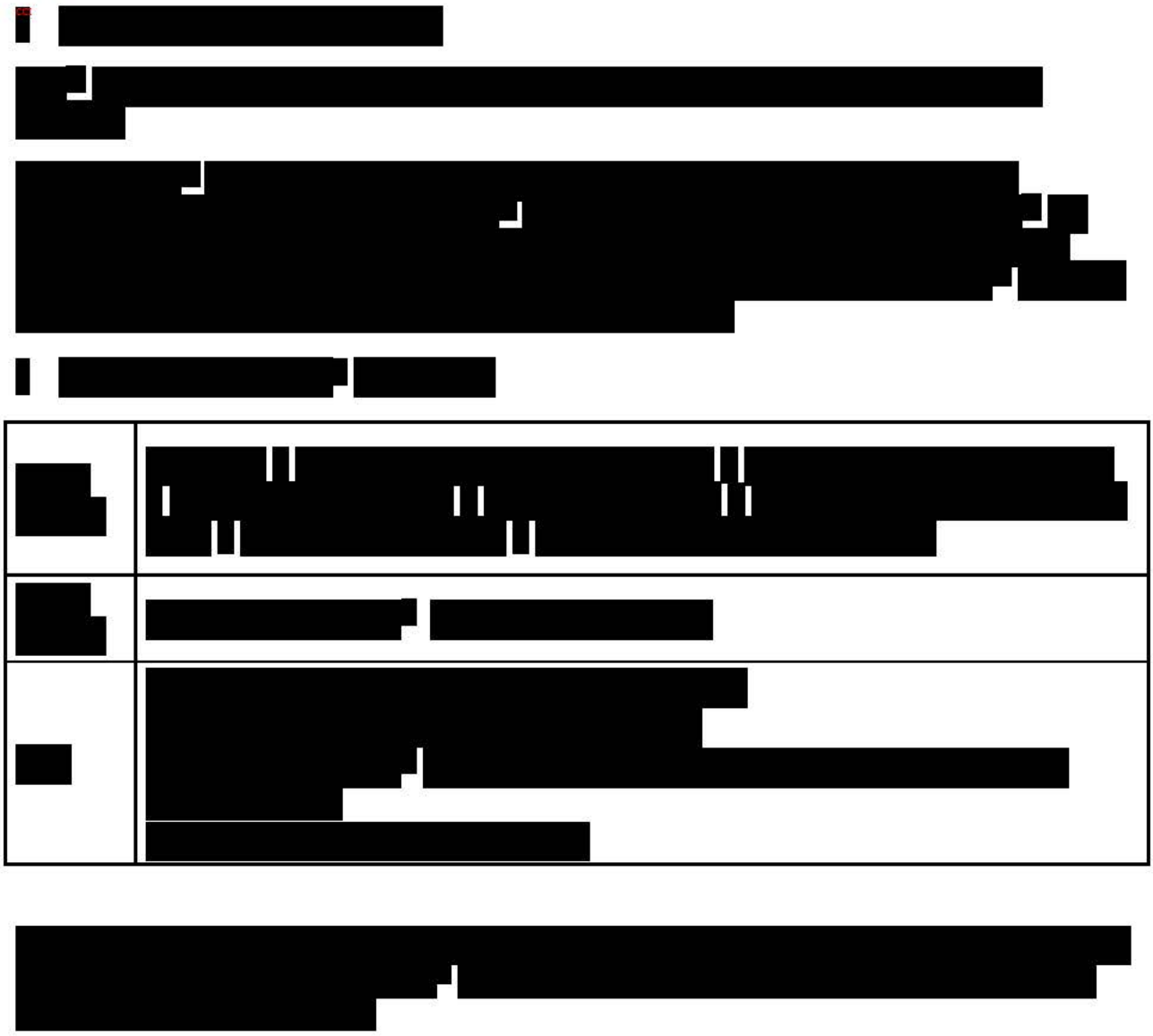
CTCAE v4.03	CTCAE Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
CCI					
CCI					
Activated partial thromboplastin time (APTT) prolonged	>ULN 1.5 x ULN	>1.5 2.5 x ULN	>2.5 x ULN; hemorrhage		
CCI					
CCI					
Hypercalcemia	Corrected serum calcium of >ULN 11.5 mg/dL; >ULN 2.9mmol/L; Ionized calcium >ULN 1.5 mmol/L	Corrected serum calcium of >11.5 12.5 mg/dL; >2.9 3.1 mmol/L; Ionized calcium >1.5 1.6 mmol/L; symptomatic	Corrected serum calcium of >12.5 13.5 mg/dL; >3.1 3.4 mmol/L; Ionized calcium >1.6 1.8 mmol/L; hospitalization indicated	Corrected serum calcium of >13.5 mg/dL; >3.4 mmol/L; Ionized calcium >1.8 mmol/L; life threatening consequences	Death
Hypocalcemia	Corrected serum calcium of <LLN 8.0 mg/dL; <LLN 2.0 mmol/L; Ionized calcium <LLN 1.0 mmol/L	Corrected serum calcium of <8.0 7.0 mg/dL; <2.0 1.75 mmol/L; Ionized calcium <1.0 0.9 mmol/L; symptomatic	Corrected serum calcium of <7.0 6.0 mg/dL; <1.75 1.5 mmol/L; Ionized calcium <0.9 0.8 mmol/L; hospitalization indicated	Corrected serum calcium of <6.0 mg/dL; <1.5 mmol/L; Ionized calcium <0.8 mmol/L; life threatening consequences	Death
Chronic kidney disease	eGFR (estimated Glomerular Filtration Rate) or CrCl (creatinine clearance) <LLN 60 ml/min/ 1.73 m2 or proteinuria 2+ present; urine protein/creatinine >0.5	eGFR or CrCl 59 30 ml/min/ 1.73 m2	eGFR or CrCl 29 15 ml/min/ 1.73 m2	eGFR or CrCl <15 ml/min/ 1.73 m2; dialysis or renal transplant indicated	Death
Creatinine increased	>1 1.5 x baseline; >ULN 1.5 x ULN	>1.5 3.0 x baseline; >1.5 3.0 x ULN	>3.0 baseline; >3.0 6.0 x ULN	>6.0 x ULN	
CCI					

CTCAE v4.03	CTCAE Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
increased					
Hyperglycemia	Fasting glucose value >ULN 160 mg/dL; Fasting glucose value >ULN 8.9 mmol/L	Fasting glucose value >160 250 mg/dL; Fasting glucose value >8.9 13.9 mmol/L	>250 500 mg/dL; >13.9 27.8 mmol/L; hospitalization indicated	>500 mg/dL; >27.8 mmol/L; life threatening consequences	Death
Hypoglycemia	<LLN 55 mg/dL; <LLN 3.0 mmol/L	<55 40 mg/dL; <3.0 2.2 mmol/L	<40 30 mg/dL; <2.2 1.7 mmol/L	<30 mg/dL; <1.7 mmol/L; life threatening consequences; seizures	Death
Hemoglobin increased	Increase in >0 2 gm/dL above ULN or above baseline if baseline is above ULN	Increase in >2 4 gm/dL above ULN or above baseline if baseline is above ULN	Increase in >4 gm/dL above ULN or above baseline if baseline is above ULN		
International normalized ratio (INR) increased	>1 1.5 x ULN; >1 1.5 times above baseline if on anticoagulation	>1.5 2.5 x ULN; >1.5 2.5 times above baseline if on anticoagulation	>2.5 x ULN; >2.5 times above baseline if on anticoagulation		
Hyperkalemia	>ULN 5.5 mmol/L	>5.5 6.0 mmol/L	>6.0 7.0 mmol/L; hospitalization indicated	>7.0 mmol/L; life threatening consequences	Death
Hypokalemia	<LLN 3.0 mmol/L	<LLN 3.0 mmol/L; symptomatic; intervention Indicated	<3.0 2.5 mmol/L; hospitalization indicated	<2.5 mmol/L; life threatening consequences	Death
Lymphocyte count decreased	<LLN 800/mm3; <LLN 0.8 x 10e9 /L	<800 500/mm3; <0.8 0.5 x 10e9 /L	<500 200/mm3; <0.5 0.2 x 10e9 /L	<200/mm3; <0.2 x 10e9 /L	
Hyper magnesemia	>ULN 3.0 mg/dL; >ULN 1.23 mmol/L		>3.0 8.0 mg/dL; >1.23 3.30 mmol/L	>8.0 mg/dL; >3.30 mmol/L; life threatening consequences	Death
Hypo magnesemia	<LLN 1.2 mg/dL; <LLN 0.5 mmol/L	<1.2 0.9 mg/dL; <0.5 0.4 mmol/L	<0.9 0.7 mg/dL; <0.4 0.3 mmol/L	<0.7 mg/dL; <0.3 mmol/L; life threatening consequences	Death
Neutrophil count decreased	<LLN 1500/mm3; <LLN 1.5 x 10e9 /L	<1500 1000/mm3; <1.5 1.0 x 10e9 /L	<1000 500/mm3; <1.0 0.5 x 10e9 /L	<500/mm3; <0.5 x 10e9 /L	
Hypo phosphatemia	<LLN 2.5 mg/dL; <LLN 0.8 mmol/L	<2.5 2.0 mg/dL; <0.8 0.6 mmol/L	<2.0 1.0 mg/dL; <0.6 0.3 mmol/L	<1.0 mg/dL; <0.3 mmol/L; life threatening consequences	Death
Platelet count decreased	<LLN 75,000/mm3; <LLN 75.0 x 10e9 /L	<75,000 50,000/mm3; <75.0 50.0 x 10e9 /L	<50,000 25,000/mm3; <50.0 25.0 x 10e9 /L	<25,000/mm3; <25.0 x 10e9 /L	
Hypernatremia	>ULN 150 mmol/L	>150 155 mmol/L	>155 160 mmol/L; hospitalization	>160 mmol/L; life threatening	Death

CTCAE v4.03	CTCAE Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
			indicated	consequences	
Hyponatremia	<LLN 130 mmol/L		<130 120 mmol/L	<120 mmol/L; life threatening consequences	Death
Hyperuricemia	>ULN 10 mg/dL (0.59 mmol/L) without physiologic consequences		>ULN 10 mg/dL (0.59 mmol/L) with physiologic consequences	>10 mg/dL; >0.59 mmol/L; life threatening consequences	Death
White blood cell (WBC) decreased	<LLN 3000/mm3; <LLN 3.0 x 10e9 /L	<3000 2000/mm3; <3.0 2.0 x 10e9 /L	<2000 1000/mm3; <2.0 1.0 x 10e9 /L	<1000/mm3; <1.0 x 10e9 /L	

a. Note: Refer to Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03, which can be found at https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE 4.03/CTCAE 4.03 2010 06 14 QuickReference 8.5x11.pdf

Appendix 3. Noninvasive markers for Fibrosis



- **Fibrosis-4 (FIB-4) Index Calculation:**

FIB-4 **Index** round ((age × AST) / (platelet × sqrt (ALT)), 0.01);

- **AST to Platelet Ratio Index (APRI) Calculation:**

APRI round (AST/ASTULN × 100 / platelet, 0.1);

Note: for FIB-4 index and APRI calculation, the laboratory parameters need to be measured from the same blood draw. Age should be the actual age at the date when laboratory values are taken.

- **NAFLD fibrosis score (NFS) Calculation:**

NFS -1.675 + 0.037 × age (years) + 0.094 × BMI (kg/m^2) + 1.13 × IFG (impaired fasting glucose) / pre-diabetes or diabetes (yes 1,no 0) + 0.99 × AST / ALT ratio - 0.013 × platelet (×10^9/L) - 0.66 × albumin (g/dL). Keep 3 decimal places.

The laboratory parameters need to be measured from the same blood draw. The last non-missing BMI on or prior to laboratory date should be used. Age should be the actual age at the date when laboratory values are taken. Status of pre-diabetes/diabetes should also be decided on the laboratory date. If a subject had pre-diabetes/diabetes at baseline, the pre-diabetes/diabetic status will be yes for all the postbaseline visits. If the subject does not have pre-diabetes/diabetes at baseline, the pre-diabetic/diabetic status will be determined based on the start date AEs of pre-diabetes and diabetes, and the collection date when fasting glucose is greater than 100 (IFG). If the AE start date or the fasting glucose collection date is on or prior to the laboratory date of a specific visit, then the pre-diabetic/diabetic status will be yes for that visit and later visits. If the day of the AE start date is missing, it will be imputed using the 1st day of the month.

The categories of NFS to be presented will be < -1.455, -1.455 to < 0.676, and > 0.676.

Appendix 4. Liver Function Prognostic Scores

- **MELD Score Calculation**

MELD score 3.78 [Ln total bilirubin (mg/dL)] + 11.2 [Ln INR] + 9.57 [Ln serum creatinine (mg/dL)] + 6.43. If the serum creatinine, the total bilirubin or the INR value is < 1.00 mg/dL, the calculation will use 1.00 as the test value. If the serum creatinine is > 4.00 mg/dL or subjects on dialysis, the calculation will use 4.00 as the serum creatinine value.

Appendix 5. Health Related Quality of Life Score Calculation

- **SF-36**

Scoring of the SF-36 scales will be performed as described in Chapter 6 of the SF-36 Health Survey Manual and Interpretation Guide, Version 2. Summary will be done for 8 domains of the SF-36 (physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health), and for the physical component score and mental component summary.

- **CLDQ-NAFLD**

CLDQ-NAFLD scores are calculated using subject responses to 36 questions in the questionnaire. If Ri is the score for the patient's response to the item i, for i 1, 2, …., 36 then the 6 domain scores are calculated as follows:

Abdominal Mean of {R1, R5, R17}

Fatigue Mean of {R2, R4, R8, R11, R13, R35}

Systemic Mean of {R3, R6, R21, R23, R27, R36}

Activity Mean of {R7, R9, R14, R30, R31}

Emotion Mean of {R10, R12, R15, R16, R19, R20, R24, R26, R34}

Worry Mean of {R18, R22, R25, R28, R29, R32, R33}

Here "Mean" is the average of nonmissing items (SAS mean function). Each score is calculated only if at least half of corresponding items are not missing. Otherwise, the score will be missing.

Overall CLDQ score is calculated by taking the mean of 6 domain scores {abdominal, fatigue, systemic, activity, emotion, worry}. Overall CLDQ score will be summarized.

- **WPAI: NASH**

The response to Question 1 of this questionnaire provides the binary endpoint whether or not the subject had been in a paid employment during the week prior to assessment.

If the subject had been in a paid employment (Response to Q1 is "Yes") at the visit when questionnaire was given, then following three scores are derived:

Percent work time missed (Absenteeism) $100 \times Q2 / (Q2 + Q4)$

Percent impairment while working (Presenteeism) $100 \times Q5 / 10$

Percent work productivity loss

$$100 \times \left[\frac{Q2}{(Q2+Q4)} + \left(1 \quad \frac{Q2}{Q2+Q4)} \right) \times \frac{Q5}{10} \right]$$

Question 6 is applicable to all subjects:

Percent activity impairment 100 × Q6 / 10.

Percent work productivity loss and percent activity impairment will be summarized.

GS-US-384-3914 Cohort 10-11 SAP

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Clinical Research eSigned	27-Aug-2019 16:00:34
PPD	Biostatistics eSigned	27-Aug-2019 18:25:36