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:	CILO (cilofexor, GS-9674); FIR (firsocostat, GS-0976)
Study Number:	GS-US-384-3914
Protocol Version (Date):	Amendment 12: 11 September 2019
Analysis Type:	Final Analysis, Cohorts 12-13
Analysis Plan Version:	Version 1.0
Analysis Plan Date:	27 January, 2021
Analysis Plan Author(s):	PPD

CONFIDENTIAL AND PROPRIETARY INFORMATION

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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
CAP	controlled attenuation parameter
CI	confidence interval
CLDQ	chronic liver disease questionnaire
CILO	Cilofexor (GS-9674)
CK	creatine kinase
CK-18	cytokeratin-18
COVID-19	corona virus disease 2019
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
ELF	enhanced liver fibrosis
ET	early termination
FAS	Full Analysis Set
FENO	fenofibrate
FIB-4	fibrosis-4
FIR	Firsocostat (GS-0976)
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
CCI	[redacted]
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
PK	pharmacokinetics
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

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 final analysis for the clinical study report (CSR) for Study GS-US-384-3914, Cohorts 12 and 13. This SAP is based on study protocol amendment 12 dated 11 September 2019 and the electronic case report form (eCRF). This SAP is for the analyses of Cohorts 12 and 13, and includes Cohorts 12 and 13 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 NAFLD/NASH.

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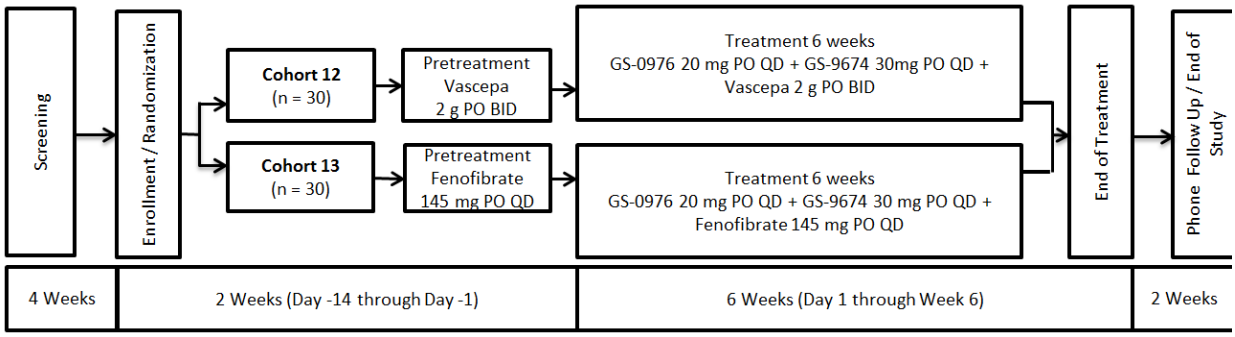
1.2. Study Design

For Cohorts 12 and 13, eligible subjects will be randomized to receive pretreatment with Vascepa 2 g twice daily or fenofibrate 145 mg once daily from Day -14 to Day -1 and will be treated with CILO 30 mg once daily, FIR 20 mg once daily, and Vascepa® 2 g twice daily; or CILO 30 mg once daily, FIR 20 mg once daily, and fenofibrate 145 mg once daily for 6 weeks as shown in the figure below.

Treatment with Vascepa or fenofibrate will be initiated 2 weeks prior to dosing with CILO and FIR with the goal of lowering pretreatment triglyceride concentrations in order to mitigate possible increases in triglycerides that result from combination treatment with CILO and FIR .



* GS-0976 = FIR; GS-9674 = CILO.

Approximately 60 subjects will be randomized (1:1) into either Cohort 12 or 13. Randomization will be stratified by screening serum triglyceride levels ([≥ 150 mg/dL and < 250 mg/dL] or [≥ 250 mg/dL and < 500 mg/dL]).

- Cohort 12 (CILO 30 mg once daily + FIR 20 mg once daily+ Vascepa 2 g twice daily) will consist of 30 subjects

- Cohort 13 (CILO 30 mg once daily + FIR 20 mg once daily + fenofibrate 145 mg once daily) will consist of 30 subjects

1.3. Sample Size and Power

For Cohorts 12 and 13, it was assumed that among subjects with baseline hypertriglyceridemia (serum triglycerides ≥ 150 mg/dL and < 500 mg/dL), treatment with CILO+FIR once daily will lead to a mean increase in serum triglycerides of 60 mg/dL from baseline after 6 weeks of treatment. Assuming that the coadministration of Vascepa or fenofibrate with CILO+FIR will mitigate this increase in serum triglycerides and that the standard deviation for serum triglycerides after 6 weeks of treatment is 120 mg/dL, a sample size of 30 subjects in each cohort will provide 85% power to detect any increase based on a one-sided t-test at a significance level of 0.05.

2. TYPE OF PLANNED ANALYSIS

This SAP is for the analyses of Cohorts 12 and 13 data only.

2.1. Interim Analyses

2.1.1. DMC Interim Analysis

There will be no formal DMC review for Cohorts 12 and 13. Therefore, no analyses will be conducted for the DMC.

2.1.2. Interim Analysis

No formal interim analysis was planned from protocol.

2.2. Final Analysis

After all subjects in Cohorts 12 and 13 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. Pretreatment Phase

Pretreatment Phase is the phase when subjects take only Vascepa or fenofibrate study drug. It starts from the date of first dose of Vascepa or fenofibrate to the date before the first dose of CILO and FIR.

3.1.2. Treatment Phase

Treatment Phase is the phase when subjects take CILO+FIR study drugs and through the follow-up visit. It starts from the date of first dose of CILO+FIR to the end of study.

3.1.3. Entire Study

Entire Study is the combination of the Pretreatment 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

The All Randomized Analysis Set includes all subjects who were randomized into Cohort 12 or 13 of this study.

3.2.2. Full Analysis Set

The Full Analysis Set (FAS) includes all subjects who were randomized into either Cohort 12 or 13 and took at least 1 dose of CILO+FIR.

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 CILO+FIR.

This is the primary analysis set for safety analyses. This analysis set will be used for safety analysis for Treatment Phase and Entire Study.

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3.2.5. Pretreatment Safety Analysis Set

The Pretreatment Safety Analysis Set includes all subjects who received at least 1 dose of Vascepa or fenofibrate in the Pretreatment Phase.

This is the analysis set for Pretreatment 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, Pretreatment 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 Pretreatment Phase, subjects in the Pretreatment Safety Analysis Set will be analyzed and will be grouped into the following:

1) Vascepa 2 g PO BID

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) CILO 30 mg PO QD + FIR 20 mg PO QD + Vascepa 2 g PO BID

4) CILO 30 mg PO QD + FIR 20 mg PO QD + 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])

3.5. Examination of Subject Subgroups

Subgrouping of subjects based on pretreatment baseline triglyceride levels 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.

- Pretreatment baseline triglyceride level ([< 250 mg/dL] or [≥ 250 mg/dL])

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 7.5.

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 CILO+FIR 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 CILO+FIR, 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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[redacted]

3.9. Analysis Visit Windows

3.9.1. Definition of Study Day

3.9.1.1. Study Day in Pretreatment Phase

Pretreatment study day will be calculated from the first dosing date of Vascepa or fenofibrate and derived as follows:

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

Therefore, Pretreatment study day 1 is the day of first dose of Vascepa or fenofibrate administration.

3.9.1.2. Study Day in Treatment Phase

Study day will be calculated from the first dosing date of CILO+FIRand derived as follows:

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

Therefore, study day 1 is the day of first dose of CILO+FIR 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 CILO+FIR. CCI [redacted] 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 in Section 3.9.2.2 unless the nominal visit name is Follow-Up (FU).

For the Pretreatment 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 Vascepa or fenofibrate. Only selected safety analysis will be conducted for the Pretreatment Phase and for the Entire Study. Selected safety lab data collected up to and including the first dosing date of CILO + FIR will be mapped according to the analysis window specified in Section 3.9.2.1 and summarized for the Pretreatment 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 Pretreatment 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 CILO+FIR. The analysis windows for selected safety data as specified in Section 7.2.1.2 are provided in Table 3-1.

Table 3-1. Pretreatment Phase Safety Analysis Visit Windows for Chemistry, Hematology, Coagulation Labs, and CCI

Analysis Visit	Nominal Pretreatment Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Pretreatment Baseline	1	(none)	1
Day 1	15	2	≥ 15 if didn't take CILO+FIR
			1st dosing date of CILO+FIR if took CILO+FIR

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 CCI [redacted] CCI

Table 3-2. Treatment Phase Analysis Visit Windows for Vital Signs, CCI Chemistry, Hematology, Coagulation Panel, CCI , 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 and ApoB

Analysis Visit	Nominal Study Day	Visit Window Study Day	
		Lower Limit	Upper Limit
Baseline	1	(none)	1
Week 4	29	2	35
Week 6	43	36	≥ 43

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

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 pretreatment study day or study day. Instead, the mapped analysis visits in both phases will be renamed as in Table 3-3 for entire study safety analysis. The pretreatment baseline is to be mapped to overall baseline.

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

Pretreatment/Treatment Phase Analysis Visit	Entire Study Analysis Visit
Pretreatment Baseline	Overall Baseline
Day 1	Overall Week 2
Week 4	Overall Week 6
Week 6	Overall Week 8

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.

[redacted]

- 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.

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:

- Pretreatment Safety Analysis Set
- Completed pretreatment study drug
- Did not complete pretreatment study drug with reasons for premature discontinuation of pretreatment study drug
- Safety Analysis Set
- Full Analysis Set
- Completed study drug
- Did not complete study drug with reasons for premature discontinuation of study drug
- [redacted]
- 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 triglyceride levels (< 250 mg/dL vs ≥ 250 mg/dL) at between screening and at pretreatment 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 Pretreatment Phase (Vascepa or fenofibrate only) by treatment group for the Pretreatment Safety Analysis Set, and for the Entire Study (CILO+FIR and Vascepa or fenofibrate) by treatment group for the Safety Analysis Set.

Total duration of exposure to Vascepa or fenofibrate in the Pretreatment Phase will be defined as the last dosing date of Vascepa or fenofibrate in the pretreatment phase or the date prior to the first dosing date of CILO+FIR, whichever is earlier, minus the first dosing date of Vascepa or fenofibrate plus 1 divided by 7, regardless of any temporary interruption in Vascepa or fenofibrate administration.

Total duration of exposure to study drug for the Entire Study will be summarized separately for Vascepa or fenofibrate, CILO, and FIR, 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 Pretreatment Phase: 1 day, 1 week, 2 weeks, and the following time periods in the Treatment Phase: 1 day, 1 week, 4 weeks and 6 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%.

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 an important protocol deviation.

4.4. Assessment of COVID-19 Impact

This study was ongoing during the novel coronavirus (2019 nCOV [COVID-19]) pandemic which has caused a disruption in the regular visit schedules for this study. Some subjects were unable to attend onsite visits due to shelter in place guidelines, site closures, or other reasons. This section provides how to handle special situations due to COVID-19 in the analysis.

4.4.1 Study Drug or Study Discontinuation Due to COVID-19

A similar summary as described in subject enrollment and disposition section of reasons for discontinuing study drug or study due to COVID-19 will be provided by treatment group and overall.

A by-subject listing of reasons for premature study drug or study discontinuation due to COVID-19 will be created.

4.4.2 Protocol Deviations Due to COVID-19

Similar summary as described in protocol deviations section will be performed for important protocol deviations due to COVID-19. The number and percentage of subjects with non-important protocol deviations related to COVID-19 by number of deviations (e.g., at least 1, with 1, 2, 3 or more deviations) will be summarized by treatment group.

A by-subject listing will be provided for subjects with important protocol deviation related to COVID-19. A separate listing will be provided for subjects with non-important protocol deviation related to COVID-19.

4.4.3. Missed and Virtual Visits due to COVID-19

A summary of subjects affected by the COVID-19 pandemic will be provided for each scheduled study visit by treatment group and overall. For each visit the summary will present the number and percentage of subjects who missed the visit due to COVID-19 or had a virtual visit due to COVID-19. For each column, the denominator for the percentage calculation will be the total number of subjects in the safety population for that column.

A by-subject listing of subjects with missed or virtual visits due to COVID-19 will be provided by subject ID number in ascending order .

Information regarding missed or virtual visits due to COVID-19 was collected as free text in the CRF comment fields. The determination of missing or virtual visits due to COVID-19 was done using Natural Language Processing (NLP) to search the CRF comment fields. A detailed explanation of the algorithm is given in Appendix 5.

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 CILO+FIR.

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 CILO+FIR. 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)
- Diabetes mellitus (absence or presence)
- Smoking status
- Screening triglyceride level category ([$\geq$ 150 mg/dL and $<$ 250 mg/dL] or [$\geq$ 250 mg/dL and $<$ 500 mg/dL])
- Pretreatment triglyceride level ($<$ 250 mg/dL or $\geq$ 250mg/dL)
- Pretreatment baseline (Day -14) triglycerides (mg/dL)
- Fasting triglycerides (mg/dL)
- Total cholesterol (mg/dL)
- High density lipoprotein -cholesterol (HDL-C) (mg/dL)
- Calculated fasting non-HDL-C (equal to total cholesterol minus HDL-C) (mg/dL)

- Calculated fasting very low density lipoprotein cholesterol (VLDL-C) (mg/dL) (equal to triglycerides divided by 5. If the triglyceride level is greater than 400 mg/dl, VLDL will not be calculated.)
- Calculated fasting low density lipoprotein cholesterol (LDL-C) (equal to non-HDL-C minus VLDL-C) (mg/dL)
- APRI
- FIB-4
- NFS
- NFS category (< -1.455, -1.455 to < 0.676, and ≥ 0.676)
- MELD score
- Albumin (g/dL)

[redacted]

- International normalized ratio (INR)
- Fasting glucose (mg/dL)
- Hemoglobin A1c (%)

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.

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[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, or 4 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.

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 Global Patient Safety 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 12 and 13 will be summarized separately for the Pretreatment Phase and the Treatment Phase, as well as summarized for the Entire Study.

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

- Any AEs with an onset date on or after the Vascepa or fenofibrate start date and no later than the date before the first dosing date of CILO+FIR
- Any AEs leading to premature discontinuation of Vascepa or fenofibrate in the Pretreatment 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 CILO+FIR start date and no later than 30 days after permanent discontinuation of any 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 Vascepa or fenofibrate start date and no later than 30 days after permanent discontinuation of any 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 Vascepa or 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 Pretreatment 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 Vascepa or 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 CILO+FIR

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 CILO+FIR, 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 any 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 Vascepa or 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 any 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 Vascepa or fenofibrate, will be considered to be treatment emergent in the Pretreatment Phase and in Entire Study; moreover, if the stop date is later than the first dosing date of CILO+FIR, 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 Vascepa or fenofibrate will be considered treatment emergent in the Pretreatment 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 CILO+FIR, it will also be considered treatment emergent in the Treatment Phase.

7.1.6. Summaries of Adverse Events and Deaths

The AEs will be summarized separately for the following phases. The Treatment Phase will include the most detailed summaries, while only selected summaries will be generated for either the Pretreatment Phase or Entire Study. Refer to detailed information in section 7.1.6.1-7.1.6.3.

- Treatment Phase (in Safety Analysis Set)
- Pretreatment Phase (in Pretreatment Safety Analysis Set)
- Entire Study (Safety Analysis Set)

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 TEAE 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 Pretreatment Phase

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

A brief, high-level summary of AEs as generated for the treatment phase will be provided for the Pretreatment 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 Pretreatment 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 Pretreatment 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 Pretreatment Safety Analysis Set for the Pretreatment Phase analysis and will include data collected up to the first dosing date of CILO+FIR. 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 any 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 Treatment Phase and the Entire Study. Values falling outside of the relevant reference range and/or having a severity grade of 1 or higher on CTCAE version 5.0 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]

Descriptive statistics will be provided by treatment group for creatinine, creatinine clearance using the Cockcroft-Gault equation, white blood cells, neutrophils, lymphocytes, hemoglobin, and platelets, and 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 CILO+FIR. 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 Pretreatment Phase and in the Entire Study

Descriptive statistics will be provided by treatment group for the lipid panel, CCI [redacted] albumin, creatinine, and creatinine clearance using the Cockcroft-Gault equation for the Pretreatment Phase and for Entire Study.

A baseline laboratory value for these 2 periods will be defined as the last measurement obtained on or prior to the date of first dose of Vascepa or fenofibrate, and referred to as the pretreatment baseline. Change from pretreatment 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.

7.2.2. Graded Laboratory Values

The CTCAE Version 5.0 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.

CCI [redacted]

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 any 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 Pretreatment Phase

Treatment-emergent laboratory abnormalities in the Pretreatment Phase are defined as values that increase at least 1 toxicity grade from pretreatment baseline at any post pretreatment baseline time point, up to and including the date of first dose of CILO+FIR. If the relevant pretreatment baseline laboratory value is missing, any abnormality of at least Grade 1 observed within the time frame specified above for the Pretreatment 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 pretreatment baseline at any post pretreatment baseline time point, up to and including the date of last dose of any 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 any 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 Pretreatment Phase

Treatment-emergent marked laboratory abnormalities in the Pretreatment Phase are defined as values that increase at least 3 toxicity grade from pretreatment baseline at any post pretreatment baseline time point up to and including the date of first dose of CILO+FIR. If the relevant pretreatment baseline laboratory value is missing, any Grade 3 or 4 values observed within the time frame specified above for the Pretreatment 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 pretreatment baseline at any post pretreatment baseline time point, up to and including the date of last dose of any 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 pretreatment baseline and each scheduled post pretreatment baseline visit for the Pretreatment 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 pretreatment baseline abnormality grade for the Pretreatment 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 pretreatment baseline values for the Pretreatment Phase and the Entire Study.

By-subject listings of treatment-emergent Grade 3 or 4 and marked laboratory abnormalities will be provided by subject ID number, and postbaseline visit in chronological for Treatment Phase, and post pretreatment baseline visit for Entire Study. The listings will include all test results that were collected throughout the study for the lab test of interest, with all applicable severity grades displayed.

CCI [redacted]

[redacted]

7.2.4. Additional Summary of Laboratory Value

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

- Pretreatment baseline values
- Values at each post pretreatment baseline visit
- Change from baseline at each post pretreatment baseline visit

Fasting triglycerides grade measured during the Pretreatment 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 Pretreatment Safety Analysis Set. A similar summary further subgrouped by pretreatment baseline triglyceride level will also be generated.

7.3. Sensitivity Analysis

Local laboratory test results were collected during the study due to COVID-19 for a few patients. Primary analysis will only include cenral laboratory results collected through Covance without additional specifying. Sensitivity analysis will be performed as summary for selected laboratory parameters by including both central and local laboratory results.

In laboratory parameters listings, all available central and local labs will be listed.

7.4. 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 CILO+FIR. 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.

7.5. 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.

7.5.1. Prior Medications

Prior medications are defined as any medications taken before a subject took the first dose of Vascepa or 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 Vascepa or 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 Vascepa or 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 Pretreatment Safety Analysis Set. No formal statistical testing is planned.

7.5.2. Concomitant Medications

Concomitant medications are defined as medications taken while a subject took study drug. Concomitant medications will be summarized separately for the Pretreatment Phase based on the Pretreatment 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 Vascepa or fenofibrate and continued to be taken after the first Vascepa or fenofibrate dosing date, or started after the first Vascepa or fenofibrate dosing date but prior to the first dosing date of CILO+FIR will be considered concomitant medications in the Pretreatment Phase. Any medication with a start date prior to or on the first dosing date of CILO+FIR and continued to be taken after the first CILO+FIR dosing date, or started after the first CILO+FIR dosing date but prior to the last dosing date of CILO+FIR 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 Vascepa or fenofibrate/CILO+FIR will also be considered concomitant in the Pretreatment/Treatment Phase. Medications with a stop date prior to the date of first dosing date of Vascepa or fenofibrate or a start date after the first dosing date of CILO+FIR will be excluded from the concomitant medication summary for the Pretreatment Phase. Medications with a stop date prior to the date of the first dosing date of CILO+FIR or a start date after the last dosing date

of CILO+FIR 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 CILO+FIR start date will be excluded from the concomitant medication summary for the Pretreatment Phase, and any medication with the month and year (if day is missing) or year (if day and month are missing) after the CILO+FIR 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.

7.6. Electrocardiogram Results

7.6.1. Investigator Electrocardiogram Assessment

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

7.7. Other Safety Measures

No additional safety measures are specified in the protocol.

7.8. Changes From Protocol-Specified Safety Analyses

CTCAE version 4.03 will be used for the severity garde of AEs. While CTCAE 5.0 will be used for the severity grade of lab abnormalities.

[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 12 and 13

	Screen[a]	Pretreatment Period/ Enrollment	Treatment Period		End of Treatment	ET	Phone Follow-Up	ET Phone Follow-Up
		D-14	D1[b]	D28(W4)(±3d)	D42 (W6) (±3d)	ET	D56 (W8) (±5d)	2 Weeks After Last Dose
ClinicalAssessment								
Informed Consent	X							
Determine Eligibility[c]	X	X						
Medical History	X	X						
Assess Ascites and Hepatic Encephalopathy	X							
CPTScore	X							
Physical Examination	X	X[d]	X[d]	X[d]	X[d]	X[d]		
Vital Signs	X	X	X	X	X	X		
Height	X							
CCI								
12-leadECG	X				X	X		
Adverse Events	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X
Dispense Vascepa® (Cohort12)		X	X					
Dispense Fenofibrate (Cohort13)		X						
Dispense FIR and CILO			X	X				
Review of Study Drug Dosing Compliance (Pill Count)			X[e]	X	X			

	Screen[a]	Pretreatment Period/ Enrollment	Treatment Period		End of Treatment	ET	Phone Follow-Up	ET Phone Follow-Up
		D-14	D1[b]	D28(W4)(±3d)	D42 (W6) (±3d)	ET	D56 (W8) (±5d)	2 Weeks After Last Dose
Chemistry	X	X	X	X	X	X		
Hematology	X	X	X	X	X	X		
Coagulation Panel	X	X	X	X	X	X		
Pregnancy Test[f]	X	X	X	X	X	X	X	X
CCI								
ApoA1,ApoB, NMRLipoprofile		X	X	X	X	X		
CCI								
Hemoglobin A1c	X		X					
Urine Drug Screening	X							
HIV-1, HBV & HCV Serology	X							
Genomic Sample[j]			X					
CCI								

a Screening assessments to be completed within 4 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 6 months of the Screening Visit for subjects without compensated cirrhosis (F4) or within 12 months of the Screening Visit for subjects with compensated cirrhosis (F4); or review of historical MRE or historical FibroScan® obtained within 6 months of the Screening Visit.
d Symptom driven physical examination.
e Vascepa® (Cohort 12) or fenofibrate (Cohort 13) only
f Females of childbearing potential only: Serum pregnancy testing at screening, urine pregnancy testing will occur at D-14, D1, D28, D42, and 2 weeks after last dose of study drug. Home urine pregnancy test for Phone Follow-Up will be provided at the D42 Visit or ET Visit.
CCI
j Genomic Sample collected for subjects who have not opted out of sample collection. No additional blood will be drawn.

Appendix 2. CTCAE Grade for Laboratory Parameters

CTCAE 5.0	CTCAE Grade				
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Anemia	Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated	Life-threatening consequences; urgent intervention indicated	Death
Activated partial thromboplastin time prolonged	>ULN - 1.5 x ULN	>1.5 - 2.5 x ULN	>2.5 x ULN; bleeding	-	-
CCI					
CCI					
Blood bicarbonate decreased	<LLN and no intervention initiated	-	-	-	-
Blood bilirubin increased	>ULN - 1.5 x ULN if baseline was normal; > 1.0 - 1.5 x baseline if baseline was abnormal	>1.5 - 3.0 x ULN if baseline was normal; >1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 10.0 x ULN if baseline was normal; >3.0 - 10.0 x baseline if baseline was abnormal	>10.0 x ULN if baseline was normal; >10.0 x baseline if baseline was abnormal	-
Cholesterol high	>ULN - 300 mg/dL; >ULN - 7.75 mmol/L	>300 - 400 mg/dL; >7.75 - 10.34 mmol/L	>400 - 500 mg/dL; >10.34 - 12.92 mmol/L	>500 mg/dL; >12.92 mmol/L	-
CPK increased	>ULN - 2.5 x ULN	>2.5 x ULN - 5 x ULN	>5 x ULN - 10 x ULN	>10 x ULN	-
Creatinine increased	>ULN - 1.5 x ULN	>1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	>3.0 x baseline; >3.0 - 6.0 x ULN	>6.0 x ULN	-

CTCAE 5.0	CTCAE Grade				
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
CCI					
Haptoglobin decreased	<LLN	-	-	-	-
Hemoglobin increased	Increase in >0 - 2 g/dL	Increase in >2 - 4 g/dL	Increase in >4 g/dL	-	-
INR increased	>1.2 - 1.5; >1 - 1.5 x baseline if on anticoagulation; monitoring only indicated	>1.5 - 2.5; >1.5 - 2.5 x baseline if on anticoagulation; dose adjustment indicated	>2.5; >2.5 x baseline if on anticoagulation; bleeding	-	-
Lipase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN; >2.0 - 5.0 x ULN and asymptomatic	>2.0 - 5.0 x ULN with signs or symptoms; >5.0 x ULN and asymptomatic	>5.0 x ULN and with signs or symptoms	-
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	-
Lymphocyte count increased	-	>4000/mm3 - 20,000/mm3	>20,000/mm3	-	-
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	-
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	-
Serum amylase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN; >2.0 - 5.0 x ULN and asymptomatic	>2.0 - 5.0 x ULN with signs or symptoms; >5.0 x ULN and asymptomatic	>5.0 x ULN and with signs or symptoms	-
White blood cell 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	-
Hypercalcemia	Corrected serum calcium of >ULN - 11.5 mg/dL; >ULN - 2.9 mmol/L; Ionized	Corrected serum calcium of >11.5 - 12.5 mg/dL; >2.9 - 3.1 mmol/L; Ionized	Corrected serum calcium of >12.5 - 13.5 mg/dL; >3.1 - 3.4 mmol/L; Ionized calcium	Corrected serum calcium of >13.5 mg/dL; >3.4 mmol/L;	Death

CTCAE 5.0	CTCAE Grade				
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
	calcium >ULN - 1.5 mmol/L	calcium >1.5 - 1.6 mmol/L; symptomatic	>1.6 - 1.8 mmol/L; hospitalization indicated	Ionized calcium >1.8 mmol/L; life-threatening consequences	
Hyperkalemia	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L; intervention initiated	>6.0 - 7.0 mmol/L; hospitalization indicated	>7.0 mmol/L; life-threatening consequences	Death
Hypermagnesemia	>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
Hypernatremia	>ULN - 150 mmol/L	>150 - 155 mmol/L; intervention initiated	>155 - 160 mmol/L; hospitalization indicated	>160 mmol/L; life-threatening consequences	Death
Hypertriglyceridemia	150 mg/dL - 300 mg/dL; 1.71 mmol/L - 3.42 mmol/L	>300 mg/dL - 500 mg/dL; >3.42 mmol/L - 5.7 mmol/L	>500 mg/dL - 1000 mg/dL; >5.7 mmol/L - 11.4 mmol/L	>1000 mg/dL; >11.4 mmol/L; life-threatening consequences	Death
Hyperuricemia	>ULN without physiologic consequences	-	>ULN with physiologic consequences	Life-threatening consequences	Death
Hypoalbuminemia	<LLN - 3 g/dL; <LLN - 30 g/L	<3 - 2 g/dL; <30 - 20 g/L	<2 g/dL; <20 g/L	Life-threatening consequences; urgent intervention indicated	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
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
Hypokalemia	<LLN - 3.0 mmol/L	Symptomatic with <LLN - 3.0 mmol/L; intervention indicated	<3.0 - 2.5 mmol/L; hospitalization indicated	<2.5 mmol/L; life-threatening consequences	Death
Hypomagnesemia	<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

CTCAE 5.0	CTCAE Grade				
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Hyponatremia	<LLN - 130 mmol/L	125-129 mmol/L and asymptomatic	125-129 mmol/L symptomatic; 120-124 mmol/L regardless of symptoms	<120 mmol/L; life-threatening consequences	Death

a. Note: Refer to Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0, which can be found at https://evs nci.nih.gov/ftp1/CTCAE/CTCAE_5.0.

CCI [redacted]

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. Determing Missing and Vitrual Visits due to COVID-19

This appendix describes the site collection of COVID-19 data as pertains to missed/virtual visits and the data processing algorithm used to determine which visits were missing and which visits were virtual.

Data collection

A COVID-19 supplement to the eCRF Completion Guidelines (CCG) was provided by data management to instruct clinical trial sites with respect to data entry expectations pertaining to scenarios related to the COVID-19 pandemic. If a visit was missed, sites should enter "Visit missed due to COVID-19." If an in-person visit was conducted virtually, sites should enter "Virtual visit due to COVID-19."

Determination of Missed and Virtual visits

Natural Language Processing (NLP) was used to search the CRF comment fields to identify instances of "COVID-19" (or synonyms, see Appendix Table 1) and "Virtual" (or synonyms, see Appendix Table 1). The search terms are maintained in a global lookup table and can be modified to tune the NLP model. For any comments with COVID-19 search terms, assign "Missed visit" or "Virtual visit as follows:

i) If COVID-19 terms are identified through NLP and the visit date is missing, then result is "Missed Visit"

ii) If COVID-19 and Virtual terms are identified through NLP for a visit, then result is "Virtual Visit". When there are multiple records for the same subject and the same visit, NLP will be based on multiple records to ensure 1 unique category per subject per visit

iii) Otherwise result is missing

Appendix Table 1. Examples of search terms for "COVID-19" and "Virtual" used to identify missed and virtual visits.

Search terms for "COVID-19"	Search terms for "Virtual"
COVID19	VIRTUAL
CORONA	TELEMED
CORONAVIRUS	TELEHEALTH
PANDEMIC	TELEPHONE
OUTBREAK	REMOTE
CRISIS	TELEMEDICINE
LOCKDOWN	TELECONSULTATION
QUARANTINE	TELEPHONICALLY
SHELTER	PHONE
	HOME VISIT
	ZOOM
	SKYPE

GS-US-384-3914 Cohort 12-13 SAP

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Clinical Research eSigned	01-Feb-2021 22:35:11
PPD	Biostatistics eSigned	02-Feb-2021 06:54:28