# STATISTICAL ANALYSIS PLAN

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| **Study Title:** | A Proof of Concept, Open-Label Study Evaluating the Safety, Tolerability, and Efficacy of Monotherapy and Combination Regimens in Subjects with Nonalcoholic Steatohepatitis (NASH) |
| **Name of Test Drugs:** | Semaglutide® (SEMA)<br>Firsocostat (FIR; GS-0976)<br>Cilofexor (CILO; GS-9674) |
| **Study Number:** | GS-US-454-5533 |
| **Protocol Version (Date):** | Original: 17 May 2019<br>Amendment 1: 16 August 2019<br>Amendment 2: 22 October 2019 |
| **Analysis Type:** | Final Analysis |
| **Analysis Plan Version:** | Version 1.0 |
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| **Analysis Plan Author(s):** | PPD |

**CONFIDENTIAL AND PROPRIETARY INFORMATION**

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| | |
|---|---|
| AE | adverse event |
| ALP | alkaline phosphatase |
| ALT | alanine aminotransferase |
| ApoA1 | apolipoprotein A1 |
| APRI | aspartate transaminase to platelet ratio index |
| AST | aspartate aminotransferase |
| BLQ | below the limit of quantitation |
| BMI | body mass index |
| CAP | controlled attenuation parameter |
| CCG | case report form completion guidelines |
| CLDQ | chronic liver disease questionnaire |
| CLDQ-NAFLD | Chronic Liver Disease Questionnaire-Nonalcoholic Fatty Liver Disease |
| CI | confidence interval |
| CILO | Cilofexor |
| CK-18 | cytokeratin 18 |
| COVID-19 | corona virus disease 2019 |
| CP | Child-Pugh |
| CRF | case report form |
| CRP | C-reactive protein |
| CSR | clinical study report |
| CTCAE | common toxicity criteria for adverse events |
| DILI | Drug Induced Liver Injury |
| DNL | de novo lipogenesis |
| ECG | Electrocardiogram |
| eCRF | electronic case report form |
| eGFR | estimated glomerular filtration rate |
| ELF™ | Enhanced Liver Fibrosis |
| ET | early termination |
| EQ-5D | EuroQoL five dimensions |
| FAS | full analysis set |
| FGF19 | fibroblast growth factor 19 |
| FIR | Firsocostat |
| FU | follow-up |
| GGT | gamma glutamyl transferase |
| GSI | Gilead Sciences, Inc. |
| HA | hyaluronic acid |
| HbA1c | hemoglobin A1c |
| HBV | hepatitis B virus |

| | |
|---|---|
| HCV | hepatitis C virus |
| HDL | high-density lipoprotein |
| HE | hepatic encephalopathy |
| HIV | human immunodeficiency virus |
| HLGT | high-level group term |
| HLT | high-level term |
| HOMA-IR | homeostasis model assessment of insulin resistance |
| HRQoL | Health-related quality of life |
| IDMC | internal data monitoring committee |
| INR | International normalized ratio |
| LDL | low-density lipoprotein |
| LLT | lower-level term |
| LOQ | limit of quantitation |
| MDRD | Modification of Diet in Renal Disease |
| 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 | nonalcoholic fatty liver disease |
| NASH | nonalcoholic steatohepatitis |
| NFS | nonalcoholic fatty liver disease fibrosis score |
| NLP | natural language processing |
| PIIINP | procollagen type III amino-terminal propeptide |
| PK | Pharmacokinetic |
| PT | preferred term |
| Q1 | first quartile |
| Q3 | third quartile |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SD | standard deviation |
| SEMA | Semaglutide® |
| SOC | System Organ Class |
| TE | treatment-emergent |
| TEAE | treatment-emergent adverse event |
| TIMP1 | tissue inhibitor of metalloprotease 1 |
| ULN | upper limit of the normal range |
| VAS | Visual Analog Scale |
| VLDL | very low-density lipoprotein |
| WBC | white blood cell |
| 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 in the clinical study report (CSR) for Study GS-US-454-5533. This SAP is based on the study protocol amendment 2 dated 22 October 2019 and the electronic case report form (eCRF). The SAP will be finalized before database finalization. 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.

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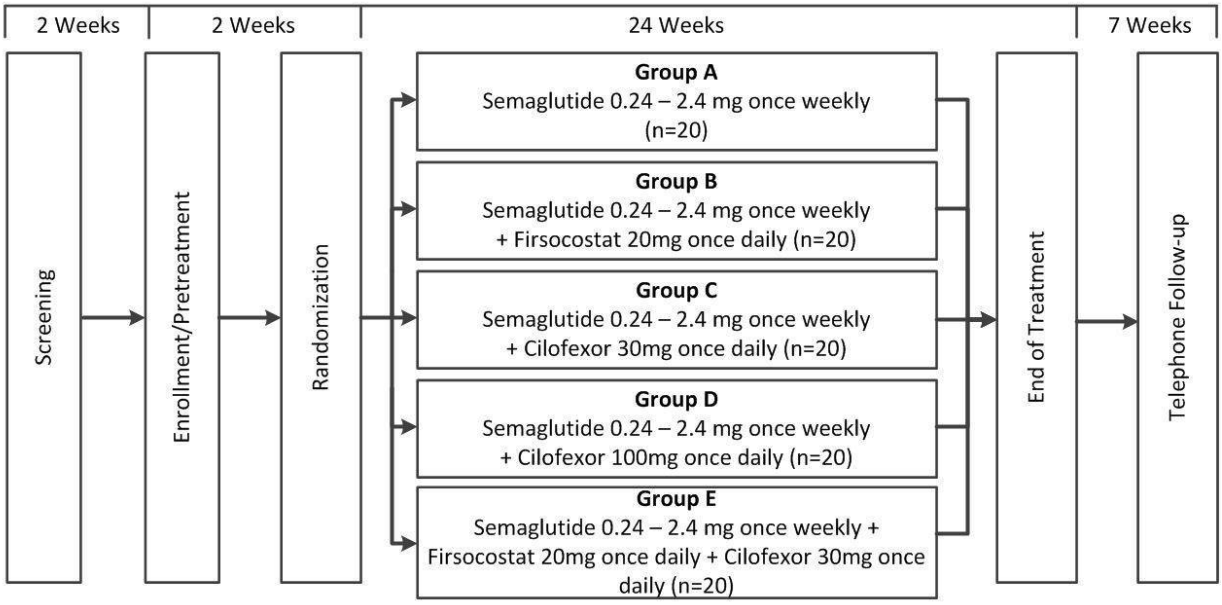
## 1.2. Study Design

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

Males or females between 18 and 75 years of age with noncirrhotic NASH may be eligible for entry (refer to the protocol for complete inclusion and exclusion criteria).

A total of approximately 100 Subjects meeting the study's entry criteria will be randomly assigned in a 1:1:1:1:1 ratio to 1 of 5 treatment groups, with approximately 20 subjects in each group, as shown in Figure 1-1.

**Figure 1-1. Overall Study Design**




Centralized randomization will be used. Randomization will be stratified by the presence or absence of type 2 diabetes mellitus, as determined by medical history or based on the screening laboratory values if previously undiagnosed (hemoglobin A1c [HbA1c] ≥ 6.5%).

Adverse events (AEs) and concomitant medications will be documented at each visit throughout the entire study. Imaging assessments (FibroScan including CAP, MRI-PDFF and MRE) and laboratory assessments of FibroTest, ELF test score and HbA1c will be performed at Screening and at Weeks 12 and 24. Other laboratory assessments will include serum chemistry, hematology, coagulation panel and estimated glomerular filtration rate (eGFR) at Screening, Day -14, Day 1 and at Weeks 1, 4, 8, 12, 16, 20 and 24; and insulin and lipids at Screening, Day 1 and at Weeks 4, 8, 12 and 24. Pregnancy testing will occur at Screening, Day 1, every 4 weeks thereafter through Week 24 and at 7 weeks posttreatment. The complete schedule of assessments is included in Appendix 1.

## 1.3. Sample Size and Power

Due to the exploratory nature of this study, the sample size was not determined by any formal power calculation. The number of subjects in each treatment group was decided based on clinical experience with other similar proof-of-concept studies.

# 2. TYPE OF PLANNED ANALYSIS

## 2.1. Data Monitoring Committee Analyses

An internal Data Monitoring Committee (IDMC) within Gilead Sciences, Inc. (GSI) will review the progress of the study and perform interim reviews of safety data in order to protect subject welfare and preserve study integrity. The IDMC will be notified of any case of suspected Drug Induced Liver Injury (DILI) by the Medical Monitor. To ensure the best interests of the participants, the IDMC will recommend to the study team whether the nature, frequency, and severity of adverse effects associated with the study treatment warrant the early termination of the study, the continuation of the study, or the continuation of the study with modifications.

The initial review will be conducted after the first 25 randomized subjects either have completed the Week 12 visit assessments or have prematurely discontinued study treatment. Subsequent IDMC meetings will be held on an ad hoc basis. The frequency of meetings can be adjusted if deemed necessary by the IDMC. Documentation of such change may be done in the meeting minutes or a note to file without an amendment to the charter.

The IDMC's role and responsibilities and the scope of analysis to be provided to the IDMC are provided in a mutually agreed upon charter, which defines the IDMC membership, meeting logistics, and meeting frequency.

## 2.2. Interim Analyses

No administrative interim analyses will be performed during the study to support publications or interactions with regulatory agencies.

## 2.3. Final Analysis

After all subjects have completed or prematurely discontinued 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 for each subject. Age, sex at birth, race, and ethnicity will be included in the listings, as space permits.

## 3.1. 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 eligible for inclusion will be summarized by treatment group.

A listing of reasons for exclusion from analysis sets will be provided by subject.

### 3.1.1. All Randomized Analysis Set

The All Randomized Analysis Set includes all subjects who were randomized in the study.

### 3.1.2. Full Analysis Set

The Full Analysis Set (FAS) includes all randomized subjects who took at least 1 dose of any study drug. This is the primary analysis set for efficacy analyses.

### 3.1.3. Safety Analysis Set

The Safety Analysis Set includes all subjects who took at least 1 dose of study drug. This is the primary analysis set for safety analyses.

### 3.1.4. Pharmacokinetic Analysis Set

The Pharmacokinetic (PK) Analysis Set includes all randomized subjects who took at least 1 dose of any study drug and have at least 1 nonmissing concentration value reported by the PK laboratory. The PK Analysis Set will be used for the listing of concentration data.

## 3.2. 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, subjects will be grouped according to actual treatment received. The actual treatment received will differ from the randomized treatment only when the actual treatment differs from randomized treatment for the entire treatment duration.

## 3.3. Strata and Covariates

Subjects will be randomly assigned to treatment groups via the interactive mobile/web response system (IXRS) using a stratified randomization schedule. Randomization will be stratified by the presence or absence of type 2 diabetes mellitus, as determined by medical history or based on the screening laboratory values if previously undiagnosed (hemoglobin A1c [HbA1c] ≥ 6.5%).

If there are discrepancies in stratification factor values between the IXRS and the clinical database, the values recorded in the clinical database will be used for analyses.

## 3.4. Examination of Subject Subgroups

There are no prespecified subject subgroupings for efficacy analyses.

## 3.5. Multiple Comparisons

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

## 3.6. Missing Data and Outliers

### 3.6.1. Missing Data

In general, missing data will not be imputed unless methods for handling missing data are specified.

For missing last dose 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 7.1.6.2, and for prior and concomitant medications in Section 7.4.

### 3.6.2. Outliers

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

## 3.7. 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) 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 date of birth and the Day 1 visit date will be used instead. If a randomized subject was not dosed with any study drug, the randomization date will be used instead of the Day 1 visit date. For subjects who were enrolled but not randomized, enrollment date will be used instead of the Day 1 visit date. For screening 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 LOQ will be used to calculate descriptive statistics if the datum is reported in the form of "< x" (where x is considered the 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 LOQ will be used to calculate descriptive statistics if the datum is reported in the form of "> x" (where x is considered the 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).

If methods based on the assumption that the data are normally distributed are not adequate, analyses may be performed on transformed data (eg, log-transformed data) or nonparametric analysis methods may be used, as appropriate.

Sparse PK concentration values that are below the limit of quantitation (BLQ) will be presented as "BLQ" in the data listing.

When any ELF component (hyaluronic acid, procollagen III N-terminal propeptide [PIIINP], and tissue inhibitor of metalloproteinase 1 [TIMP1]) is below the lower LOQ or above the upper LOQ, the ELF test score will be calculated based on the imputed value of the component(s) as defined in Appendix 4.

## 3.8. Analysis Visit Windows

### 3.8.1. Definition of Study Day

The first dose date of individual study drug will be calculated separately for each study drug (ie, SEMA, FIR and CILO) within a treatment group. Study Day 1 is defined as the first dose date of any study drug, which is the minimum of the first dose dates of individual study drugs within a treatment group. Therefore, Study Day 1 is the day of first dose of any study drug.

Study day will be calculated from the first dose date of any study drug and derived as follows:

- For postdose study days: Assessment Date  First Dose Date of Any Study Drug + 1
- For days prior to the first dose: Assessment Date  First Dose Date of Any Study Drug

### 3.8.2. 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.

In general, the baseline value will be the last nonmissing value on or prior to the first dose date of any study drug. For Health-Related Quality of Life (HRQoL) questionnaire data, nominal baseline values will be used.

On-treatment visit windows will be calculated from Study Day 1 for selected efficacy measures, vital signs, electrocardiogram (ECG) and safety laboratory data.

Efficacy (except for imaging) and safety data, collected up to and including the last dose date + 30 days, will be mapped according to the following analysis windows.

All patient-reported HRQoL questionnaire data will not be windowed, but rather analyzed according to their nominal visits. Also, missing baseline values will not be imputed.

The analysis windows for imaging (liver stiffness as measured by transient elastography [including CAP], MRI-PDFF, and MRE), HOMA-IR (based on insulin and plasma glucose),

lipid profile (total cholesterol, high-density lipoprotein [HDL] cholesterol, fasting triglycerides, fasting low-density lipoprotein [LDL] cholesterol, fasting non-HDL cholesterol, fasting very low-density lipoprotein [VLDL] cholesterol), HbA1c, FibroTest (and components), and ELF test score (and components) are provided in Table 3-1 and Table 3-2.

**Table 3-1. Analysis Visit Windows for Imaging, HbA1c, FibroTest (and Components), and ELF Test Score (and Components)**

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

**Table 3-2. Analysis Visit Windows for Plasma Glucose, Insulin, HOMA-IR, and Lipids**

| Nominal Visit | Nominal Day | Lower Limit | Upper Limit |
|---|---|---|---|
| Baseline | 1 | (none) | 1 |
| Week 4 | 29 | 2 | 42 |
| Week 8 | 57 | 43 | 70 |
| Week 12 | 85 | 71 | 126 |
| Week 24 | 169 | 127 | ≥ 169 |

The analysis windows for vital signs (eg, systolic and diastolic blood pressure), weight, and laboratory data including chemistry (eg, ALT, AST, bilirubin, GGT, and ALP), hematology, and coagulation panel are provided in Table 3-3.

**Table 3-3. Analysis Visit Windows for Vital Signs, Weight, and Laboratory Data**

| Nominal Visit | Nominal 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 | 126 |
| Week 20 | 141 | 127 | 154 |
| Week 24 | 169 | 155 | ≥ 169 |

The analysis windows for calculated Child-Pugh (CP) score are provided in Table 3-4.

**Table 3-4. Analysis Visit Windows for CP Score**

| Nominal Visit | Nominal Day | Lower Limit | Upper Limit |
|---|---|---|---|
| Baseline | 1 | (none) | 1 |
| Week 4 | 29 | 2 | 42 |
| Week 8 | 57 | 43 | 70 |
| Week 12 | 85 | 71 | 98 |
| Week 16 | 113 | 99 | 126 |
| Week 20 | 141 | 127 | 154 |
| Week 24 | 169 | 155 | ≥ 169 |

The analysis windows for 12-lead ECG are provided in Table 3-5.

**Table 3-5. Analysis Visit Windows for 12-lead ECG**

| Nominal Visit | Nominal Day | Lower Limit | Upper Limit |
|---|---|---|---|
| Baseline | 1 | (none) | 1 |
| Week 24 | 169 | 2 | ≥ 169 |

Data relating to unscheduled visits or ET visits may be assigned to a particular visit or time point based on the visit windows. The following conventions will be used:

- An unscheduled visit prior to the first dose of any study drug may be included in the calculation of the baseline value, if applicable.
- Unscheduled visits after the first dose of any study drug will be included in determining the maximum postbaseline toxicity grade.

### 3.8.3. 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, continuous 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 dose date of any study drug 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 ECG findings) for categorical data.

- 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 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 chosen for analysis.

If multiple, valid, nonmissing measurements from transient elastography for liver stiffness exist in an analysis visit window, records will be chosen based on the following rules if a single value is needed:

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

- For postbaseline visits, measurements by the same probe type (XL or M) as baseline will be selected. If no measurement by the same probe type as baseline is available, the analysis value for the corresponding postbaseline visit will be considered as missing. If there are multiple records by the same probe type at baseline, the rules to choose postbaseline continuous measurements described above will apply.

- Controlled attenuation parameter (CAP) data will be analyzed if the liver stiffness data are available from the same record of transient elastography.

# 4. SUBJECT DISPOSITION

## 4.1. Subject Enrollment and Disposition

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

A similar enrollment table will be provided for the All Randomized Analysis Set by randomization stratum. The denominator for the percentage of subjects in the stratum will be the total number of randomized subjects. If there are discrepancies in the value used for stratification assignment between the IXRS and the clinical database, the value collected in the clinical database will be used for the summary. A listing of subjects with discrepancies in the value used for stratification assignment between the IXRS and the clinical database at the time of data finalization will be provided.

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 overall. This summary will present the number of subjects screened, the number of subjects enrolled, the number of subjects enrolled but not randomized, the number of subjects randomized, the number of subjects randomized but never treated, and the number of subjects in each of the categories listed below:

- Safety Analysis Set
- FAS
- PK Analysis Set
- Completed study drug
- Did not complete study drug with reasons for premature discontinuation of study drug
- 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 Safety Analysis Set corresponding to that column. In addition, a flowchart will be provided to depict the disposition at the final analysis.

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)
- Lot number and/or bottle ID

A summary of subjects affected by the corona virus disease 2019 (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 and those who 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.

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 6.

A by-subject listings will be provided by subject ID number in ascending order to support the above summary table.

## 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 to the study drug specified in the protocol.

### 4.2.1. Duration of Exposure to Study Drug

The last dose date of individual study drug will be calculated separately for each study drug in a treatment group, and will be the end date on the study drug administration case report form (CRF) for the record where the “study drug was permanently withdrawn” flag is ‘Yes’.

Total duration of exposure to individual study drug that is administered daily (ie, FIR and CILO) will be defined as last dose date of individual study drug minus first dose date of individual study drug plus 1. Total duration of exposure to individual study drug that is administered weekly (ie, SEMA) will be defined as last dose date of individual study drug minus first dose date of individual study drug plus 7. Total duration of exposure to treatment regimen will be defined as the maximum of [(last dose date of SEMA plus 6) and last dose date(s) of daily administered individual study drug(s)] minus first dose date of any study drug plus 1. Total duration of exposure will be calculated regardless of any temporary interruptions in study drug administration, and will be expressed in weeks using up to 1 decimal place (eg, 4.5 weeks).

Total duration of exposure to treatment regimen (weeks) [maximum of (last dose date of SEMA + 6, last dose date[s] of daily administered individual study drug[s]) first dose date of any study drug + 1] / 7

Total duration of exposure to daily administered individual study drug (weeks) (last dose date of individual study drug first dose date of individual study drug + 1) /7

Total duration of exposure to weekly administered individual study drug (weeks) (last dose date of individual study drug first dose date of individual study drug + 7) /7

If the last study drug dose 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 analysis. At the time of any interim analysis (eg, DMC), the missing last dosing date will be imputed by the data snapshot date for subjects who are still on treatment.

The total duration of exposure to treatment regimen and the total duration of exposure to each individual study drug will be summarized using descriptive statistics. In addition, the total duration of exposure to treatment regimen will be summarized by the number (ie, cumulative counts) and percentage of subjects exposed through the following time periods: 1 day, 1 week, 4 weeks, 8 weeks, 12 weeks, 16 weeks, 20 weeks, and 24 weeks. Summaries will be provided by treatment group for the Safety Analysis Set.

No formal statistical testing is planned.

### 4.2.2. Adherence to Study Drug

For the individual study drugs that are orally administered once daily in tablet forms (ie, FIR 20 mg, CILO 30 mg, CILO 100 mg), the presumed total amount of study drug administered to a subject will be determined by the data collected on the drug accountability CRF using the following formula:

$$\text{Total Amount of Study Drug Administered} = (\sum \text{No. of Tablets Dispensed}) - (\sum \text{No. of Tablets Returned})$$

For SEMA, the presumed total amount of study drug administered to a subject will be determined by the data collected on the study drug administration CRF using the following formula:

$$\text{Total Amount of Study Drug Administered} = \sum \text{Actual Dose (mg)}$$

The total amount of study drug administered will be summarized using descriptive statistics for each individual study drug by treatment group for the Safety Analysis Set.

Prescribed adherence will be calculated. The level of prescribed adherence to the individual study drug 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 24 weeks of treatment.

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

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

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

The total amount of individual study drugs that are administered orally once daily (ie, FIR 20 mg, CILO 30 mg, CILO 100 mg) for 24 weeks will be 168 tablets. According to the SEMA dose escalation schedule, the total amount of SEMA administered for 24 weeks will be 32.96 mg.

Descriptive statistics for the level of prescribed adherence with the number and percentage of subjects belonging to adherence categories (< 75%, ≥ 75 to < 90%, ≥ 90%) will be provided for each individual study drug by treatment group for the Safety Analysis Set. The number and percentage of subjects with ≥ 75% level of prescribed adherence to all individual study drugs in a treatment group will also be provided by treatment group.

The summary of prescribed adherence will be provided. No formal statistical testing is planned.

A by-subject listing of study drug administration and drug accountability will be provided 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 were randomized 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 and the number of subjects who did not meet specific criteria 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) and baseline characteristics (body weight [in kg], height [in cm], body mass index [BMI; in $kg/m^2$] as a continuous variable and as categories [$< 30$ $kg/m^2$, and $\geq 30$ $kg/m^2$]) 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 demographic data will be provided for the Safety Analysis Set.

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 include:

- Type 2 diabetes mellitus (presence or absence; as determined by medical history or based on the screening laboratory values if previously undiagnosed [HbA1c] $\geq 6.5\%$)
- ALT (U/L)
- AST (U/L)
- Total bilirubin (mg/dL)
- Direct bilirubin (mg/dL)
- ALP (U/L)
- GGT (U/L)
- Albumin (g/dL)
- International normalized ratio (INR)
- Platelets ($\times 10^3$/uL)
- Steatosis by MRI-PDFF (%)
- Steatosis by CAP from transient elastography
- Steatosis by CAP from transient elastography (XL probe)

- Liver stiffness by MRE (kPa)
- Liver stiffness by transient elastography
- Liver stiffness by transient elastography category (< 9.9 kPa, ≥ 9.9 to < 14.0 kPa, ≥ 14.0 kPa)
- ELF test score and its components (hyaluronic acid, procollagen type III amino-terminal propeptide [PIIINP], and tissue inhibitor of metalloprotease 1 [TIMP1])
- ELF test score category (< 9.8, ≥ 9.8)
- FibroSure/FibroTest and selected components ($\alpha_2$-macroglobulin, haptoglobin, apolipoprotein A1 nephelometry)
- AST to platelet ratio index (APRI)
- Fibrosis-4 (FIB-4) Index
- FIB-4 category (< 1.30, ≥ 1.30 to < 2.67, ≥ 2.67)
- Non-alcoholic fatty liver disease fibrosis score (NFS)
- NFS category (< -1.455, ≥ -1.455 to < 0.676, ≥ 0.676)
- Model for End-Stage Liver Disease (MELD) score
- Calculated CP score
- Fasting insulin (uIU/mL)
- Fasting plasma glucose (mg/dL)
- HOMA-IR
- HbA1c (%)
- Total cholesterol (mg/dL)
- HDL cholesterol (mg/dL)
- Fasting non-HDL cholesterol (mg/dL) (ie, total cholesterol minus HDL cholesterol)
- Fasting triglycerides (mg/dL)
- Fasting VLDL cholesterol (mg/dL)

- Fasting LDL cholesterol (mg/dL)
- Systolic blood pressure (mmHg)
- Diastolic blood pressure (mmHg)
- eGFR (mL/min/1.73m$^2$) calculated by the Modification Diet in Renal Disease (MDRD) equation (protocol Section 6.10.2)

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.

By-subject listings of baseline characteristics will be provided by subject ID number in ascending order.

Methods for derivation of ELF, FIB-4, FibroSure/FibroTest, APRI, NFS, CP score and MELD score are described in Appendix 3 and Appendix 4.

### 5.3. Medical History

General medical history will be collected at screening and Day -14 for general conditions (ie, conditions not specific to the disease being studied).

General medical history data will not be coded but will be listed only.

# 6. EFFICACY ANALYSES

CCI

[redacted]

CCI

CCI

CCI [redacted]

# 7. SAFETY ANALYSES

## 7.1. Adverse Events and Deaths

### 7.1.1. Adverse Event Dictionary

Clinical and laboratory AEs will be coded using the current version of MedDRA. System organ class, 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 the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 (Appendix 2). 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. Relationship of Adverse Events to Pen-Injector

Related AEs are those for which the investigator selected "Related" on the AE CRF to the question of "Related to Pen-Injector." 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 pen-injector will be considered related for summary purposes. However, by-subject data listings will show the relationship as missing.

### 7.1.5. Serious Adverse Events

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

### 7.1.6. Treatment-Emergent Adverse Events

7.1.6.1. Definition of Treatment-Emergent Adverse Events

Treatment-emergent adverse events (TEAEs) are defined as 1 or both of the following:

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

7.1.6.2. Incomplete Dates

If the onset date of the AE is incomplete and the AE stop date is not prior to the first dose date of any study drug, then the month and year (or year alone if month is not recorded) of onset determine whether an AE is treatment-emergent (TE). The event is considered TE 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 dose date of any study drug, 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 drug

An AE with completely missing onset and stop dates, or with the onset date missing and a stop date later than the first dose date of any study drug, will be considered to be TE. 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 dose date of any study drug will be considered TE.

### 7.1.7. Summaries of Adverse Events and Deaths

Treatment-emergent AEs 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 in the categories described below will be provided by treatment group. All deaths observed in the study will also be included in this summary.

The number and percentage of subjects who experienced at least 1 TEAE will be provided and summarized by SOC, HLT, PT, and treatment group as follows:

- TEAEs

For the AE categories described below, summaries will be provided by SOC, PT, and treatment group:

- TEAEs by maximum severity
- TEAEs of Grade 2 or higher by maximum severity
- TEAEs of Grade 3 or higher by maximum severity
- TE treatment-related AEs
- TE Treatment-related AEs of Grade 2 or higher by maximum severity
- TE Treatment-related AEs of Grade 3 or higher by maximum severity
- TE pen-injector related AEs
- TE SAEs
- TE treatment-related SAEs
- TEAEs leading to premature discontinuation of any study drug
- TEAEs leading to permanent discontinuation of study
- TEAEs leading to death (ie, outcome of death)
- TEAEs leading to dose modification or temporary interruption of any study drug

Multiple events will be counted only once per subject in each summary. Adverse events will be summarized and listed first in alphabetical 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, TEAEs, TEAEs of Grade 2 or higher, TEAEs of Grade 3 or higher, TE SAEs, TE treatment-related AEs, TE treatment-related AEs of Grade 2 or higher, TE treatment-related AEs of Grade 3 or higher, TE treatment-related SAEs, TEAEs leading to premature discontinuation of any study drug, and TEAEs leading to dose modification or temporary interruption of any study drug will be summarized by PT only, in descending order of total frequency.

For AEs that occurred > 30 days after the last dose date of any study drug, a brief, high-level summary of the number and percentage of subjects who experienced at least 1 such AE in the categories described below will be provided by treatment group. The following tables will also be provided with the AE categories summarized by PT only, in descending order of total frequency.

- AEs that occurred > 30 days posttreatment
- Treatment-related AEs that occurred > 30 days posttreatment
- SAEs that occurred > 30 days posttreatment

In addition, data listings will be provided for the following:

- All AEs, indicating whether the event is TE
- All AEs with severity of Grade 3 or higher
- All SAEs
- All Deaths
- AEs leading to premature discontinuation of any study drug
- AEs leading to permanent discontinuation of study
- AEs leading to dose modification or temporary interruption of any study drug
- AEs occurring greater than 30 days posttreatment

### 7.1.8. Additional Analysis of Adverse Events

The incidence of pruritus AEs will be examined between treatment groups. The following PTs will be used to identify pruritus AEs:

- pruritus
- pruritus generalized

The number and percentage of subjects who experienced any of the above events postbaseline during the study, either treatment-emergent or > 30 days posttreatment, will be summarized by PT, severity, and treatment group.

## 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 Safety Analysis Set and will include data collected up to the last dose of any study drug 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 (eg, DMC). 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. Values falling outside of the relevant reference range and/or having a severity grade of 1 or higher on the CTCAE 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

Summaries of ALT, AST, total bilirubin, direct bilirubin, GGT, ALP, platelets, eGFR using the MDRD equation, and creatinine are included in the efficacy analysis and thus they are not repeated in the safety analysis.

Descriptive statistics will be provided by treatment group for white blood cell (WBC), neutrophils, lymphocytes, and hemoglobin 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/time of first dose of study drug. 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 3.8.3.

### 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.

For baseline ALT, AST, total bilirubin, and direct bilirubin, the CTCAE version 5.0 will be used to assign toxicity grades to the derived average baseline values.

#### 7.2.2.1. Treatment-Emergent Laboratory Abnormalities

Treatment-emergent laboratory abnormalities 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 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 (eg, DMC). If the relevant baseline laboratory value is missing, any abnormality of at least Grade 1 observed within the time frame specified above will be considered TE.

Treatment-emergent laboratory abnormalities are defined as values within the reference range at baseline, but which become lower or higher than the reference range at postbaseline, or values had a directional change in abnormality from baseline (eg, the value low at baseline became high at postbaseline visit) at any postbaseline time point, up to and including the date of last dose of 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 (eg, DMC). If the relevant baseline laboratory value is missing, any postbaseline laboratory value that is lower or higher than the reference range will be considered TE.

#### 7.2.2.2. Treatment-Emergent Marked Laboratory Abnormalities

Treatment-emergent marked laboratory abnormalities 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 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 (eg, DMC). If the relevant baseline laboratory value is missing, any Grade 3 or 4 values observed within the timeframe specified above will be considered TE marked abnormalities.

#### 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.

The following summaries (number and percentage of subjects) for TE laboratory abnormalities will be provided by lab test and treatment group; subjects will be categorized according to the most severe postbaseline abnormality grade 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 up to 30 days after last dose date of any study drug.

A by-subject listing of TE 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 abnormal flags displayed.

### 7.2.3. Liver-related Laboratory Evaluations

Liver-related abnormalities after initial study drug dosing will be examined and summarized using the number and percentage of subjects who meet the criteria for close observation or for withholding study drug separately. Subjects will be grouped according to their baseline ALT or AST level into 2 subgroups: normal (ie, ≤ upper limit of the normal range [ULN]) or elevated (ie, > ULN). Laboratory tests, ALT and AST, are evaluated independently.

#### 7.2.3.1. Criteria for Close Observation

Subjects meet the criteria for close observation if they were reported to have any of the following laboratory test values for postbaseline measurements:

- For subjects with normal baseline ALT or AST:

  ALT or AST > 3 × ULN

- For subjects with elevated baseline ALT or AST:

  ALT or AST > 3 × baseline

  ALT or AST > 300 U/L

#### 7.2.3.2. Criteria for Withholding Study Drug

Subjects meet the criteria for withholding of study drug if they were reported to have any of the following laboratory test values for postbaseline measurements:

- For subjects with normal baseline ALT or AST:

  ALT or AST > 8 × ULN

  ALT or AST > 5 × ULN for 2 weeks

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

  ALT or AST > 3 × ULN and INR > 1.5 (if not on therapeutic anticoagulation)

- For subjects with elevated baseline ALT or AST:

  ALT or AST > 500 U/L

  ALT or AST > 3 × baseline or > 300 U/L and total bilirubin > 2 × ULN (or direct bilirubin > 2 × baseline in subjects with Gilbert's syndrome)

  ALT or AST > 3 × baseline or > 300 U/L and INR > 1.5 (if not on therapeutic anticoagulation)

#### 7.2.3.3. Summary of Liver-Related Laboratory Abnormalities

The summary will include data from all postbaseline visits up to 30 days after the last dose date of any study drug. The number and percentage of subjects who meet each criterion will be summarized by treatment group. For individual laboratory tests, subjects will be counted once based on the most severe postbaseline values. For the composite criteria that evaluate more than 1 lab test, subjects will be counted once when the criteria are met at the same postbaseline visit date. The denominator is the number of subjects in the Safety Analysis Set who have at least 1 nonmissing postbaseline on-treatment value of all relevant tests at the same postbaseline visit date.

A listing of subjects who met at least 1 of the above criteria will be provided.

### 7.3. Body Weight and Vital Signs

Summaries of body weight, BMI, and systolic and diastolic blood pressure are included in the efficacy analysis and thus they are not repeated in the safety analysis. For vital signs including pulse rate [beats/min] and temperature [°C], descriptive statistics will be provided by treatment group for 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 any study drug. Change from baseline to a postbaseline visit will be defined as the postbaseline value minus the baseline value. Body weight and 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 3.8.3. 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. Body weight, height and BMI will be included in a separate by-subject listing.

### 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 medication taken before a subject took the first study drug.

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 dose date of any study drug 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 medication 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. Medications with a completely missing start date will be included in the prior medication summary, unless otherwise specified.

Summaries will be based on the 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. 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 medication with a start date prior to or on the first dose date of any study drug and continued to be taken after the first dose date, or started after the first dose date but prior to or on the last dose date of any study drug will be considered concomitant medication. Medications started and stopped on the same day as the first dose date of any study drug or the last dose date of any study drug will also be considered concomitant. Medications with a stop date prior to the date of first dose date of any study drug or a start date after the last dose date of any study drug will be excluded from the concomitant medication summary. 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 will be excluded from the concomitant medication summary. 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 study drug stop date will be excluded from the concomitant medication summary. Medications with completely missing start and stop dates will be included in the concomitant medication summary, unless otherwise specified. Summaries will be based on the Safety Analysis Set. 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 shift table of the investigators' assessment of ECG results at Week 24 compared with baseline values will be presented by treatment group using the following categories: normal; abnormal, not clinically significant; abnormal, clinically significant; or missing. The number and percentage of subjects in each cross-classification group of the shift table will be presented. Subjects with a missing value at baseline or postbaseline will not be included in the denominator for percentage calculation. No formal statistical testing is planned.

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

## 7.6. Changes From Protocol-Specified Safety Analyses

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

# 8. PHARMACOKINETIC ANALYSES

## 8.1. PK Sample Collection

A single PK blood sample will be collected anytime at Week 1, Week 4, Week 8, and Week 12 for all subjects. The plasma concentrations of study drug(s) and relevant metabolite(s) may be evaluated, as applicable. PK samples may also be used to measure protein-binding of study drug(s) and/or its metabolites.

## 8.2. PK Analyses Related to Sparse PK Sampling

A population PK model may be developed to characterize the PK of study drug(s) and relevant metabolite(s). Sparse PK sampling data from this study may be combined with data from other studies in a meta-population analysis using mixed-effect modeling techniques. Details of the population PK analysis will be provided in a separate population PK analysis plan.

The following listing will be provided for all PK samples collected in this study:

- PK sampling details by subject including actual dosing time and actual draw time, calculated time postdose of sample collection, differences in scheduled and actual draw times, sample age, and sample concentration by analyte.

# 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.

# 11. SAP REVISION

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

# 12. APPENDICES

## Appendix 1. Schedule of Assessments

| | | Pretreatment Period | | | Treatment Period | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Kinetic Biomarkers (Cycle 1) | | | | | | | | | | Kinetic Biomarkers (Cycle 2) | | | | |
| | Screening | Day −14 | Day −11 (±1d) | Day −7 (±1d) | Day 1 | Day 7 (WK 1) (±3d) | Day 28 (WK 4) (±3d) | Day 56 (WK 8) (±3d) | Day 84 (WK 12) (±3d) | Day 112 (WK 16) (±3d) | Day 140 (WK 20) (±3d) | Day 154 (WK 22) (±1d) | Day 157 (WK 22 Day 2) (±1d) | Day 161 (WK 23) (±1d) | Day 168 (WK 24/EOT) (±3d)[a] | ET | Telephone Follow-Up[b] (±3d) |
| **Clinical Assessments** | | | | | | | | | | | | | | | | | |
| Written Informed Consent | X | | | | | | | | | | | | | | | | |
| Confirm Eligibility | X | X | | | | | | | | | | | | | | | |
| Medical History | X | X | | | | | | | | | | | | | | | |
| PE, Vital Signs including Weight[c] | X | X | | | X | X | X | X | X | X | X | | | | X | X | |
| Fundus Examination[d] | X | | | | | | | | | | | | | | | | |
| Height | X | | | | | | | | | | | | | | | | |
| 12-lead ECG | X | | | | | | | | | | | | | | X | X | |
| Quality of Life Questionnaires | | | | | X | | | | X | | | | | | X | | |
| Calculate CP Score | | | | | X | | X | X | X | X | X | | | | X | X | |
| Dispense Deuterated Water | | X | | | | | | | | | | X | | | | | |

| | | Pretreatment Period | | | Treatment Period | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Kinetic Biomarkers (Cycle 1) | | | | | | | | | Kinetic Biomarkers (Cycle 2) | | | | | |
| | Screening | Day −14 | Day −11 (±1d) | Day −7 (±1d) | Day 1 | Day 7 (WK 1) (±3d) | Day 28 (WK 4) (±3d) | Day 56 (WK 8) (±3d) | Day 84 (WK 12) (±3d) | Day 112 (WK 16) (±3d) | Day 140 (WK 20) (±3d) | Day 154 (WK 22) (±1d) | Day 157 (WK 22 Day 2) (±1d) | Day 161 (WK 23) (±1d) | Day 168 (WK 24/EOT) (±3d)[a] | ET | Telephone Follow-Up[b] (±3d) |
| Dispense study drugs | | | | | X[e] | | X | X | X | X | X | | | | | | |
| Review of Deuterated Water Compliance | | | | X | | | | | | | | | | X | | | |
| Review of Study Drug Dosing Compliance | | | | | | | 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 |
| Adverse Events | X[f] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| **Imaging Assessments** | | | | | | | | | | | | | | | | | |
| FibroScan® | X[g] | | | | | | | | X | | | | | | X | X[h] | |
| MRI-PDFF, MRE | X[g] | | | | | | | | X | | | | | | X | X[h] | |
| **Laboratory Assessments** | | | | | | | | | | | | | | | | | |
| Subject Fasting | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| Chemistry, Hematology, Coagulation | X | X | | | X | X | X | X | X | X | X | | | | X | X | |

| | | Pretreatment Period | | | Treatment Period | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Kinetic Biomarkers (Cycle 1) | | | | | | | | | | Kinetic Biomarkers (Cycle 2) | | | | | |
| | Screening | Day −14 | Day −11 (±1d) | Day −7 (±1d) | Day 1 | Day 7 (WK 1) (±3d) | Day 28 (WK 4) (±3d) | Day 56 (WK 8) (±3d) | Day 84 (WK 12) (±3d) | Day 112 (WK 16) (±3d) | Day 140 (WK 20) (±3d) | Day 154 (WK 22) (±1d) | Day 157 (WK 22 Day 2) (±1d) | Day 161 (WK 23) (±1d) | Day 168 (WK 24/EOT) (±3d)[a] | ET | Telephone Follow-Up[b] (±3d) |
| Insulin and Lipids | X | | | | X | | X | X | X | | | | | | X | X[h] | |
| Hemoglobin A1c (HbA1c) | X | | | | | | | | X | | | | | | X | X[h] | |
| eGFR | X | X | | | X | X | X | X | X | X | X | | | | X | X | |
| HIV-1, HBV, HCV Serology | X | | | | | | | | | | | | | | | | |
| Calcitonin | X | | | | | | | | | | | | | | | | |
| FibroTest® | X[g] | | | | | | | | X | | | | | | X | X[h] | |
| ELF™ Test[i] | X | | | | | | | | X | | | | | | X | X[h] | |
| CCI | | | | | | | | | | | | | | | | | |
| Blood Collection (Kinetic Biomarkers) | | X | X | X | X | | | | | | | X | X | X | X | | |
| PK Sampling | | | | | | X[j] | X[j] | X[j] | X[j] | | | | | | | | |
| Pregnancy Testing[k] | X | | | | X | | X | X | X | X | X | | | | X | X | X |
| Urine Drug Screen | X | | | | | | | | | | | | | | | | |

| | Screening | Pretreatment Period | | | Treatment Period | | | | | | | | | | | | Telephone Follow-Up[b] (±3d) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Kinetic Biomarkers (Cycle 1) | | | | | | | | | | Kinetic Biomarkers (Cycle 2) | | | | | |
| | | Day −14 | Day −11 (±1d) | Day −7 (±1d) | Day 1 | Day 7 (WK 1) (±3d) | Day 28 (WK 4) (±3d) | Day 56 (WK 8) (±3d) | Day 84 (WK 12) (±3d) | Day 112 (WK 16) (±3d) | Day 140 (WK 20) (±3d) | Day 154 (WK 22) (±1d) | Day 157 (WK 22 Day 2) (±1d) | Day 161 (WK 23) (±1d) | Day 168 (WK 24/EOT) (±3d)[a] | ET | |
| CCI | | | | | | | | | | | | | | | | | |
| Urine Collection (Kinetic Biomarkers) | | X | X | X | X | | | | | | | X | X | X | X | | |
| CCI | | | | | | | | | | | | | | | | | |

a Subjects prematurely discontinuing from the study should complete an ET visit within 30 days of last dose of study drugs or pretreatment deuterated water.
b Subjects that received at least one dose of study drug will be contacted for a Telephone Follow-up Visit 7 weeks after the date of the last dose
c Complete physical examination to be performed at Screening. Symptom driven physical examination to be performed at Day -14, Day 1, Day 7 (Week 1), Week 4, Week 8, Week 12, Week 16, Week 20 and Week 24 (EOT) or ET visits
d For subjects with type 2 diabetes (from medical history or from Screening Hemoglobin A1c ≥6.5%), a fundus exam will be performed at Screening. Fundus examinations require pharmacological dilation of both pupils or the use of a digital fundus photography camera specified for non-dilated examination. If a fundus examination matching this description has been performed within 90 days prior to the date of the Screening Visit, the procedure does not need to be repeated unless there has been worsening of visual function since the last examination in the opinion of the investigator. The results must be available prior to Enrollment (Day -14)
e Subject will take first dose of study drugs on-site at Day 1.
f AE reporting during Screening is limited to SAEs and AEs related to study procedures
g Required for all subjects. Will not be used to assess eligibility for subjects that meet inclusion criteria based on historical liver biopsy. If a FibroScan® and/or MRE has been performed within 4 weeks prior to the date of the Screening Visit, the procedure does not need to be repeated. Similarly, if an MRI-PDFF has been performed within 4 weeks prior to the date of the Screening Visit and is deemed acceptable by the central reader, the procedure does not need to be repeated
h At the discretion of the Investigator
i ELF™ Test score will not be provided to the sites
j Single PK sample anytime during visit
k All females of childbearing potential will have a serum pregnancy test at Screening. Urine pregnancy testing will occur at Day 1 (prior to dosing), Week 4, Week 8, Week 12, Week 16, Week 20 and Week 24 (EOT) or ET visits. All females of childbearing potential that received at least one dose of study drug will be dispensed a urine pregnancy testing kit at the Week 24 (EOT) or ET visit for home testing at the Telephone Follow-Up visit. At the Telephone Follow-Up visit, subjects will be requested to report the result of the urine pregnancy test

## Appendix 2. CTCTAE 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 | | |
| Alanine aminotransferase increased | >ULN 3.0 x ULN if baseline was normal; 1.5 3.0 x baseline if baseline was abnormal | >3.0 5.0 x ULN if baseline was normal; >3.0 5.0 x baseline if baseline was abnormal | >5.0 20.0 x ULN if baseline was normal; >5.0 20.0 x baseline if baseline was abnormal | >20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal | |
| Alkaline phosphatase increased | >ULN 2.5 x ULN if baseline was normal; 2.0 2.5 x baseline if baseline was abnormal | >2.5 5.0 x ULN if baseline was normal; >2.5 5.0 x baseline if baseline was abnormal | >5.0 20.0 x ULN if baseline was normal; >5.0 20.0 x baseline if baseline was abnormal | >20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal | |
| Aspartate aminotransferase increased | >ULN 3.0 x ULN if baseline was normal; 1.5 3.0 x baseline if baseline was abnormal | >3.0 5.0 x ULN if baseline was normal; >3.0 5.0 x baseline if baseline was abnormal | >5.0 20.0 x ULN if baseline was normal; >5.0 20.0 x baseline if baseline was abnormal | >20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal | |
| 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 | |

| CTCAE 5.0 | CTCAE Grade | | | | |
|---|---|---|---|---|---|
| **CTCAE Term** | **Grade 1** | **Grade 2** | **Grade 3** | **Grade 4** | **Grade 5** |
| 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 | |
| GGT increased | >ULN 2.5 x ULN if baseline was normal; 2.0 2.5 x baseline if baseline was abnormal | >2.5 5.0 x ULN if baseline was normal; >2.5 5.0 x baseline if baseline was abnormal | >5.0 20.0 x ULN if baseline was normal; >5.0 20.0 x baseline if baseline was abnormal | >20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal | |
| 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 | |

| CTCAE 5.0 | CTCAE Grade | | | | |
|---|---|---|---|---|---|
| **CTCAE Term** | **Grade 1** | **Grade 2** | **Grade 3** | **Grade 4** | **Grade 5** |
| 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 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 |
| 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 |

| CTCAE 5.0 | CTCAE Grade | | | | |
|---|---|---|---|---|---|
| **CTCAE Term** | **Grade 1** | **Grade 2** | **Grade 3** | **Grade 4** | **Grade 5** |
| 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 |
| 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 |

* Since anticoagulation medication is **NOT** captured in lab data, the condition for anticoagulation medication is ignored in the grade derivation.
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

## Appendix 3. Liver Function Prognostic Scores

- **Child-Pugh Score**

| | 1 | 2 | 3 |
|---|---|---|---|
| **Hepatic Encephalopathy (HE)** | **None**<br>No encephalopathy and not on any treatment for hepatic encephalopathy | **Medication-Controlled**<br>Subject is lethargic, may have moderate confusion<br><br>Subject is receiving medical therapy for HE | **Medication-Refractory**<br>Marked confusion/incoherent, rousable but sleeping or comatose |
| **Ascites** | **None**<br>No ascites and not on treatment for ascites | **Mild/Moderate**<br>Cross sectional imaging showing ascites<br><br>Abdominal distension<br><br>Medication for ascites | **Severe (diuretic-refractory)**<br>Visible clinically |
| **Total Bilirubin (mg/dL)** | < 2 | 2-3 | > 3 |
| **Albumin (g/dL)** | > 3.5 | 2.8-3.5 | < 2.8 |
| **INR** | < 1.7 | 1.7-2.3 | > 2.3 |

There are 5 components for CP score as seen in the first column. Each will be assigned a subscore ranging between 1 and 3 based on the matching condition as described in the corresponding row and the value in the header row of the corresponding column. For example, when total bilirubin value is 2.5 mg/dL, the total bilirubin subscore will be 2.

CP score is obtained by adding the subscore for each parameter, ranging between 5 and 15.

For Day 1 and postbaseline visits, HE and ascites will be from the same day as laboratory data collected. If baseline CP score is missing due to unevaluable laboratory data or discrepancy in the collection dates between HE and ascites and laboratory data, baseline CP score will be calculated using the last laboratory values collected prior to Day 1 and the last assessment results of HE and ascites prior to Day 1.

- **MELD Score**

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 4. Noninvasive Markers for Fibrosis

- **Enhanced Liver Fibrosis (ELF)**

ELF test score 2.278 + 0.851× ln (hyaluronic acid) + 0.751× ln (PIIINP) + 0.394 × ln (TIMP1);

Note: All ELF test score components (hyaluronic acid, PIIINP and TIMP1) need to be measured from the same blood draw. ELF test score will only be calculated when ELF test score is missing and components are less than the LOQ or above the upper LOQ. Individual components are to be imputed per data handling conventions in Section 3.7, and ELF test score will be calculated based on the imputed values of components.

- **FibroSURE/FibroTest**

| | |
|---|---|
| **Step-1 formula** | f5 4.467 × Log[$\alpha_2$-macroglobulin(g/L)] 1.357 × Log[Haptoglobin (g/L)] + 1.017 × Log[GGT(U/L)] + 0.0281 × [Age (year)] + 1.737 × Log [Total Bilirubin (umol/L)] 1.184 × [ApoA1 (g/L)] + 0.301 × Sex (female 0, male 1) 5.540 |
| **Step-2 formula** | FibroSURE/FibroTest® Score 1/(1+exp^(-f5)) |
| **Note** | • In the formula, SI value and units should be applied.<br>• The Log function in the formula is with base 10.<br>• FibroSURE/FibroTest score should be calculated from the parameters from the same blood draw<br>• Age is when the blood draw was taken |

Note: For subject with Gilbert's syndrome or hemolysis according to the medical history page at screening, the FibroSURE/FibroTest score will be calculated using direct bilirubin instead of total bilirubin in above formula throughout the study.

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

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

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

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)**

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-diabetic/diabetic status will be yes for all the postbaseline visits. If the subject does not have pre-diabetic/diabetes at baseline, the 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 1$^{st}$ day of the month.

## Appendix 5. Health Related QoL Score

- **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.

- **EQ-5D**

Scoring of EQ-5D will be performed as described in EQ-5D-5L user guide. Summary will be done for 5 dimensions in descriptive system (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) and the EQ Visual Analogue Scale.

## Appendix 6. Determining Missing and Virtual 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 a visit which was to be conducted in-person 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 Table X1) and "Virtual" (or synonyms, see Table X1). The search terms are maintained in a global lookup and can be modified and/or corrected to tune the NLP model. For each comment field the following algorithm was applied:

**STEP 1:** Eliminate extraneous text from each comment field, e.g. "and", "or", "for", etc. This is done using the list of extraneous terms given in Table X2.

**STEP 2:** Check each of the remaining comment text strings against the "COVID-19" terms and "Virtual" terms with the Levenshtein distance, using SAS function COMPGED (Computes a generalized edit distance using the Levenshtein operations to compute/summarize the degree of difference between two text strings):

i. If Levenshtein distance < 149 for any of the "COVID-19" terms then COVIDFL 1, else COVIDFL 0
ii. If Levenshtein distance < 149 for any of the "Virtual" terms then VIRTFL 1, else VIRTFL 0

**STEP 3:** For any comments with COVIDFL 1, assign "Missed visit" or "Virtual visit as follows:

i. IF COVIDFL 1 and the visit date is missing then result is 'Missed Visit'
ii. IF COVIDFL 1 and VIRTFL 1 then result is 'Virtual Visit'
iii. Otherwise result is missing

Table X1: 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 |

Table X2: Examples of extraneous text terms to eliminate from the comment fields.

| | | | | |
|---|---|---|---|---|
| a | down | in | she'd | Until |
| about | during | into | she'll | Up |
| above | each | is | she's | Very |
| after | few | it | should | Was |
| again | for | its | so | We |
| against | from | it's | some | we'd |
| all | further | itself | such | we'll |
| am | had | i've | than | Were |
| an | has | let's | that | we're |
| and | have | me | that's | we've |
| any | having | more | the | What |
| are | he | most | their | what's |
| as | he'd | my | theirs | When |
| at | he'll | myself | them | when's |
| be | her | nor | themselves | Where |
| because | here | of | then | where's |

| | | | | |
|---|---|---|---|---|
| been | here's | on | there | Which |
| before | hers | once | there's | While |
| being | herself | only | these | Who |
| below | he's | or | they | Whom |
| between | him | other | they'd | who's |
| both | himself | ought | they'll | Why |
| but | his | our | they're | why's |
| by | how | ours | they've | With |
| could | how's | ourselves | this | Would |
| did | i | out | those | You |
| do | i'd | over | through | you'd |
| does | if | own | to | you'll |
| doing | i'll | same | too | Your |
| down | i'm | she | under | you're |
| | you've | yourself | yourselves | Yours |

# GS-US-454-5533_SAP_Final_Analysis

## ELECTRONIC SIGNATURES

| Signed by | Meaning of Signature | Server Date (dd-MMM-yyyy hh:mm:ss) |
|---|---|---|
| PPD | Biostatistics eSigned | 07-Aug-2020 19:12:08 |
| PPD | Clinical Research eSigned | 11-Aug-2020 15:26:00 |