# 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 Drugs:** | Selonsertib (SEL, GS-4997); GS-0976; GS-9674 |
| **Study Number:** | GS-US-384-3914 |
| **Protocol Version (Date):** | Amendment 10: 13 July 2018 |
| **Analysis Type:** | Interim Analysis, Cohorts 1-9 |
| **Analysis Plan Version:** | Version 1.0 |
| **Analysis Plan Date:** | 01 August 2018 |
| **Analysis Plan Author(s):** | PPD |

**CONFIDENTIAL AND PROPRIETARY INFORMATION**

# TABLE OF CONTENTS

## LIST OF TABLES

# LIST OF ABBREVIATIONS

| | |
|---|---|
| AE | adverse event |
| ALT | alanine aminotransferase |
| ALP | alkaline phosphatase |
| ApoA1 | apolipoprotein A1 |
| AST | aspartate aminotransferase |
| BLQ | below the limit of quantitation |
| BMI | body mass index |
| C4 | 7-alpha-hydroxy-4-cholesten-3-one |
| CFR | Code of Federal Regulations |
| CI | confidence interval |
| CK-18 | cytokeratin 18 |
| CLDQ | chronic liver disease questionnaire |
| CRF | case report form |
| 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 |
| eGFR | estimated glomerular filtration rate |
| ELF | enhanced liver fibrosis |
| ET | early termination |
| FAS | Full Analysis Set |
| FGF19 | fibroblast growth factor 19 |
| FU | follow up |
| GGT | Gamma glutamyl transferase |
| Gilead | Gilead Sciences |
| HA | hyaluronic acid |
| HbA1c | hemoglobin A1c |
| HBV | hepatitis B virus |
| HCV | hepatitis C virus |
| HDL | high-density lipoprotein |
| HDL-C | HDL-cholesterol |
| HLT | high-level term |
| HLGT | high level group term |
| HOMA-IR | homeostasis model assessment of insulin resistance |
| ICH | International Conference on Harmonization (of Technical Requirements for Registration of Pharmaceuticals for Human Use) |
| INR | International normalized ratio |

| | |
|---|---|
| LDL-C | low-density lipoprotein cholesterol |
| LTT | lower-level term |
| LOQ | limit of quantitation |
| ME | multiple-echo |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MELD | Model for End-Stage Liver Disease |
| NASH | nonalcoholic steatohepatitis |
| PIIINP | procollagen III amino terminal peptide |
| PK | pharmacokinetic |
| PT | preferred term |
| Q1, Q3 | first quartile, third quartile |
| QoL | quality of life |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SD | standard deviation |
| SF-36 | short form (36) |
| SI (units) | international system of units |
| SOC | system organ class |
| TE | treatment-emergent |
| TEAE | treatment-emergent adverse event |
| TFLs | tables, figures, and listings |
| TIMP-1 | tissue inhibitor of metalloproteinase 1 |
| ULN | upper limit of normal |
| VLDL-C | very low density lipoprotein cholesterol |
| WHO | World Health Organization |
| WPAI | work productivity and activity impairment questionnaire |

# 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 interim clinical study report (CSR) for Study GS-US-384-3914, Cohorts 1 through 9. This SAP is based on the study protocol amendment 10 dated 13 July 2018 and the electronic case report form (eCRF). This SAP covers the interim analyses for Cohorts 1 through 9 and includes Cohorts 1 through 9 data only. The SAP will be finalized before database finalization of Cohorts 1 through 9. Any changes made after the finalization of the SAP will be documented in the interim CSR. There will be a separate SAP prepared for the Final Analysis.

## 1.1. Study Objectives

The primary objective of this study is as follows:

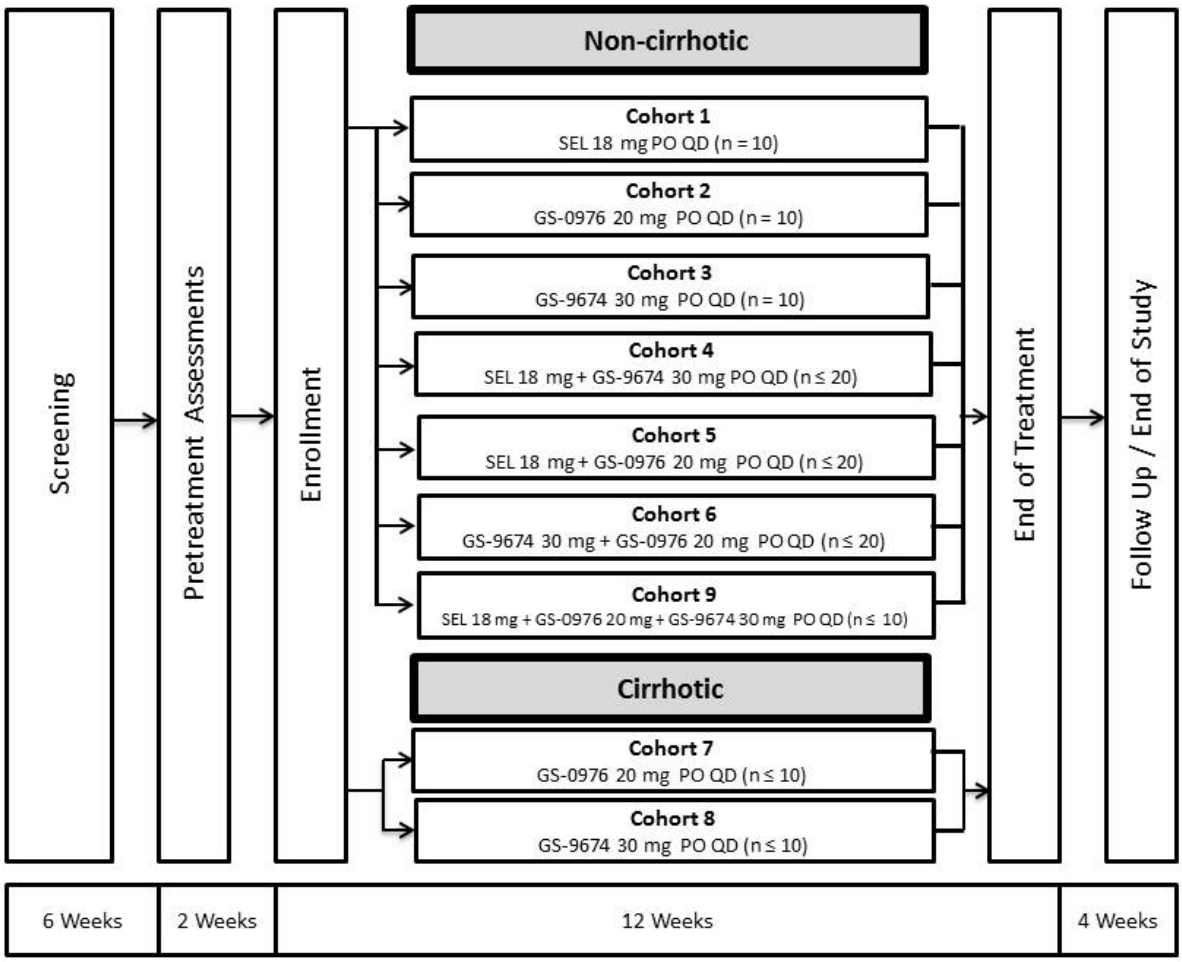
- To evaluate the safety and tolerability of study drug(s) in subjects with NASH as assessed by magnetic resonance imaging - proton density fat fraction (MRI-PDFF) and magnetic resonance elastography (MRE).

CCI [redacted]

## 1.2. Study Design

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

For Cohorts 1 through 9, eligible subjects will be enrolled to receive treatment with selonsertib (SEL; GS-4997), GS-0976, GS-9674; the combination of SEL and GS-9674, SEL and GS-0976, GS-9674 and GS-0976; or SEL, GS-0976 and GS-9674 for 12 weeks as shown in the figure below.



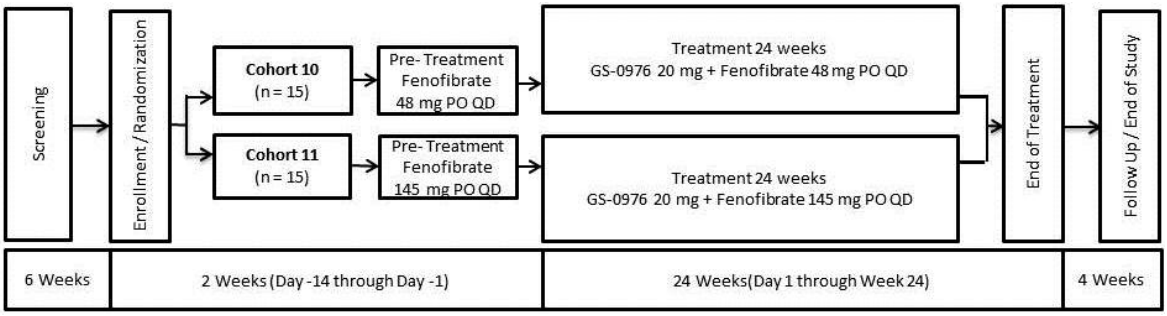

Approximately 120 subjects total will be enrolled into 1 of 9 cohorts.

- Cohort 1 (SEL) will consist of 10 enrolled subjects
- Cohort 2 (GS-0976) will consist of 10 enrolled subjects

- Cohort 3 (GS-9674) will consist of 10 enrolled subjects
- Cohort 4 (SEL + GS-9674) will consist of up to 20 enrolled subjects
- Cohort 5 (SEL + GS-0976) will consist of up to 20 enrolled subjects
- Cohort 6 (GS-0976 + GS-9674) will consist of up to 20 enrolled subjects
- Cohort 7 (GS-0976) will consist of up to 10 enrolled subjects with Child-Pugh-Turcotte (CPT) A cirrhosis
- Cohort 8 (GS-9674) will consist of up to 10 enrolled subjects with CPT A cirrhosis
- Cohort 9 (SEL + GS-0976 + GS-9674) will consist of approximately 10 enrolled subjects

Cohorts 1 through 6 and 9 will be enrolled sequentially while Cohorts 7 and 8 will be randomized in parallel.

For Cohorts 10 and 11, eligible subjects will be randomized to receive pre-treatment with fenofibrate 48 mg or fenofibrate 145 mg from Day -14 to Day -1 and will be treated with GS-0976 20 mg and fenofibrate 48 mg or GS-0976 20 mg and fenofibrate 145 mg for 24 weeks as shown in the figure below.




A total of 30 subjects will be randomized (1:1) into either Cohort 10 or 11; randomization will be stratified by (1) screening serum triglyceride levels ([≥ 150 and < 250 mg/dL] or [≥ 250 and < 500 mg/dL]), and (2) fibrosis stage [F3 defined as protocol inclusion criteria 5a - 5b; or F4 defined as inclusion criteria 5c - 5e]. Approximately 60% of subjects in each cohort should have cirrhosis (F4) based on inclusion criteria 5c – 5e. Approximately 60% subjects in each cohort should have screening serum triglycerides ≥ 150 and < 250 mg/dL as below:

- Cohort 10 (GS-0976 20 mg + fenofibrate 48 mg) will consist of 15 subjects:
  - Approximately 9 subjects with screening serum triglycerides ≥ 150 and < 250 mg/dL
  - Approximately 6 subjects with screening serum triglycerides ≥ 250 and < 500 mg/dL

- Cohort 11 (GS-0976 20 mg + fenofibrate 145 mg) will consist of 15 subjects:
  - Approximately 9 subjects with screening serum triglycerides ≥ 150 and < 250 mg/dL
  - Approximately 6 subjects with screening serum triglycerides ≥ 250 and < 500 mg/dL

### 1.3. Sample Size and Power

Due to the exploratory nature of this study, no formal power calculations were used to determine sample size in Cohorts 1 to 9. The number of subjects was chosen based on clinical experience with other similar proof of concept studies.

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

# 2. TYPE OF PLANNED ANALYSIS

## 2.1. Data Monitoring Committee Analyses

An internal Gilead data monitoring committee (DMC) will review the progress of the study and perform interim reviews of safety data for Cohorts 1 through 9, due to the sequential enrollment design. The DMC will review cumulative data from these cohorts. The DMC will be notified of any case of suspected drug-induced liver injury (DILI) by the medical monitor. The DMC will provide recommendations whether the nature, frequency, and severity of adverse effects associated with study treatment warrant early termination of the study in the best interests of the participants, whether the study should continue as planned, or the study should continue with modifications. The DMC's specific activities will be defined by a mutually agreed charter, which will define the DMC's membership, conduct, and meeting schedule.

There will be no formal DMC review for Cohorts 10 and 11. However, internal safety monitoring will be conducted continuously on an ongoing basis.

## 2.2. Interim Analyses

A formal interim analysis will be performed after subjects in the first 9 cohorts complete or early discontinue the study.

Administrative interim analyses will also be performed to support the safety review or for conferences and publications. For Cohorts 1 through 9, the administrative interim analyses will include data from the completed cohorts and also the other on-going cohorts. For Cohorts 10 and 11, the administrative interim analysis will be performed after all subjects complete 12 weeks of treatment or early discontinue treatment.

Data from Cohort 10 and 11 will not be included in this interim analysis for Cohorts 1 through 9.

## 2.3. Final Analysis

After all subjects have completed or early 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. A separate SAP will be provided to describe the statistical analyses of the final analysis.

# 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 Safety Analysis Set, unless otherwise specified, 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 subject. The treatment group to which subjects were initially assigned will be used in the listings.

## 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.

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

### 3.1.1. All Enrolled Analysis Set

All Enrolled Analysis Set includes all subjects who received a study subject identification number in the study after screening.

### 3.1.2. Full Analysis Set

The Full Analysis Set (FAS) includes all subjects who were enrolled into the study and received at least 1 dose of 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 were administered at least 1 dose of study drug. This is the primary analysis set for safety analyses.

CCI [redacted]

[redacted]

### 3.2. Subject Grouping

For analyses based on the FAS, subjects will be grouped according to the treatment to which they were assigned. 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 enrolled/randomized treatment only when their actual treatment differs from enrolled/randomized treatment for the entire treatment duration.

CCI [redacted]

### 3.3. Strata and Covariates

Cohorts 1 through 9 of this study do not use a stratified randomization schedule in enrolling subjects. No covariates will be included in efficacy and safety analyses.

### 3.4. Examination of Subject Subgroups

There are no prespecified subject subgroupings for efficacy and safety 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 dosing date of study drug, imputation rules are described in Section 4.2.1. The handling of missing or incomplete dates for AE onset is described in Section 7.1.5.2, and for prior and concomitant medications in Section 7.4.

#### 3.6.2. 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.

### 3.7. Data Handling Conventions and Transformations

In general, age in years on the date of the first dose of study drug will be used for analyses and presentation in listings. If an enrolled subject was not dosed with any study drug, the enrollment date will be used instead of the first dosing date of study drug. For screen failures, the date the informed consent was signed will be used for age calculation. If only birth year is collected on

the CRF, "01 July" will be used for the unknown birth day and month for the purpose of age calculation. If only birth year and month are collected, "01" will be used for the unknown birth day.

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 for calculation of 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 for calculation of 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 for calculation of summary statistics.

- A value that is 1 unit above the LOQ will be used for calculation of 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 for calculation of descriptive statistics if the datum is reported in the form of "≤ x" or "≥ x" (where x is considered the LOQ).

Natural logarithm transformation will be used for plasma/blood concentrations. Plasma concentration values that are below the limit of quantitation (BLQ) will be presented as "BLQ" in the concentration data listing.

### 3.8. Analysis Visit Windows

#### 3.8.1. Definition of Study Day

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

- For postdose study days: Assessment Date – First Dosing Date + 1

- For days prior to the first dose: Assessment Date – First Dosing Date

Therefore, study day 1 is the day of first dose of study drug administration.

#### 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 dosing date of study drug. For CCI [redacted], 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. The CCI will not be windowed, but rather analyzed according to their nominal visit.

Selected safety and efficacy data collected, up to and including the last dosing date + 30 days, will be mapped according to the following analysis windows unless the nominal visit name is early termination (ET) or follow-up (FU). The nominal visit name will be used for the ET and FU visits.

The analysis windows for vital signs, CCI chemistry, hematology, coagulation panel, lipid profile, homeostasis model assessment of insulin resistance (HOMA-IR), model for end-stage liver disease (MELD) score, fibroblast growth factor 19 (FGF19), 7-alpha-hydroxy-4-cholesten-3-one (C4), and apolipoprotein A1 (ApoA1) are provided in Table 3-1.

**Table 3-1. Analysis Visit Windows for Vital Signs, CCI Chemistry, Hematology, Coagulation Labs, Lipid Profiles, HOMA-IR, MELD Score, FGF19, C4, and ApoA1**

| 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 | ≥ 85 |

The analysis windows for ECG, CCI (CCI CCI tissue inhibitor of metalloproteinase 1 [PIIINP], and procollagen III amino terminal peptide [TIMP-1]) and CCI, alpha-2 Maroglobin, and haptoglobin are provided in Table 3-2.

**Table 3-2. Analysis Visit Windows for ECG, CCI CCI and its components, CCI, Alpha-2 Maroglobin, and Haptoglobin**

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

The analysis windows for CCI CCI CCI total p38, CCI MRE, and MRI-PDFF are provided in Table 3-3.

**Table 3-3. Analysis Visit Windows for CCI CCI CCI total p38, CCI MRE, and MRI-PDFF**

| Nominal Visit | Nominal Day | Lower Limit | Upper Limit |
|---|---|---|---|
| Baseline | 1 | (none) | 1 |
| Week 4 | 29 | 2 | 56 |
| Week 12 | 85 | 57 | ≥ 85 |

Data from unscheduled visits may be assigned to a particular visit based on the visit windows. The following conventions will be followed:

- An unscheduled visit prior to the first dosing of study drug may be included in the calculation of the baseline value, if applicable.
- Unscheduled visits after the first dose of study drug will be included in determining the maximum postbaseline toxicity grade.
- Data collected on a follow-up visit will be summarized as a separate visit, and labeled "Follow-up Visit" of each phase.

### 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:

- In general, the baseline value will be the last nonmissing value on or prior to the first dosing date of study drug. If multiple measurements occur on the same day, the last nonmissing value prior to the time of first dosing of study drug will be considered as the baseline value. If these multiple measurements occur at the same time or the time is not available, the average of these measurements (for continuous data) will be considered the baseline value.
- For postbaseline visits:
  - 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, unless otherwise specified.

If multiple, valid nonmissing, categorical 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 available record on or prior to the date of the first dose of study drug will be selected. If there are multiple records with the same time or no time recorded on the same day, the value with the lowest severity will be selected (eg, normal will be selected over abnormal for safety ECG findings).

- For postbaseline visits, if there are multiple records with the same time or no time recorded on the same day, the value with the worst severity within the window will be selected (eg, abnormal will be selected over normal for safety ECG findings).

# 4. SUBJECT DISPOSITION

## 4.1. Subject Enrollment and Disposition

A summary of subject disposition will be provided by treatment group. This summary will present the number of subjects screened, the number of subjects who met all eligibility criteria but were not enrolled with reasons subjects not enrolled, the number of subjects enrolled, the number of subjects enrolled but never treated, and the number of subjects in each of the categories listed below:

- Safety Analysis Set
- FAS
- [redacted]
- Continuing study drug (if applicable)
- Completed study drug
- Did not complete study drug with reasons for premature discontinuation of study drug
- Continuing study if applicable
- 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.

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)

## 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

Total duration of exposure to study drug will be defined as last dosing date minus first dosing date plus 1, 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). 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.

Total duration of exposure to study drug (weeks) = (last dose date – first dose date + 1)/7

The total duration of exposure to study drug will be summarized using descriptive statistics and percentage of subjects exposed through the following time periods: 1 day, 1 week, 2 weeks, 4 weeks, 8 weeks, and 12 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

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.

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 is greater than 100%, the result will be set to 100%.

For subjects who complete treatment, the number of doses expected to be administered for each study drug is as below:

- GS-4997: Cohorts 1, 4, 5 and 9 are expected to administer 84 doses
- GS-0976: Cohort 2 is expected to administer 168 doses (1 dose contains 10 mg GS-0976); Cohorts 5, 6, 7 and 9 are expected to administer 84 doses (1 dose contains 20 mg GS-0976)

- GS-9674: Cohort 3 is expected to administer 252 doses (1 dose contains 10 mg GS-9674); Cohorts 4, 6, 8 and 9 are expected to administer 84 doses (1 dose contains 30 mg GS-9674).

Summaries will be provided by treatment group and by study drug 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 by subject ID number (in ascending order) and visit (in chronological order).

### 4.3. Protocol Deviations

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 Enrolled Analysis Set. A by-subject listing will be provided for those subjects with any important protocol deviation.

# 5. BASELINE CHARACTERISTICS

## 5.1. Demographics

Subject demographic variables (ie, age, sex, race, and ethnicity) will be summarized by treatment group and overall using descriptive statistics for age, and using number and percentage of subjects for sex, race, and ethnicity. The summary of demographic data will be provided for the Safety Analysis Set.

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:

- height
- [redacted]
- body mass index as a continuous variable and as categories (< 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)
- albumin
- [redacted]
- [redacted]
- [redacted]
- total bilirubin
- [redacted]
- [redacted]
- fasting insulin
- fasting glucose
- homeostasis model assessment of insulin resistance (HOMA-IR)
- [redacted]

- international normalized ratio (INR)

- MELD score

- calculated fasting low density lipoprotein cholesterol (LDL-C) (= non-HDL-C minus VLDL-C)

- smoking status
- MRI-PDFF
- MRE

[redacted]

[redacted]

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 (ie, conditions not specific to the disease being studied) data will be collected at screening and only included in the listing. 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.

# 6. EFFICACY ANALYSES

All analyses will be conducted at each administrative interim analysis and repeated at the Interim Analysis for Cohorts 1 through 9 when all subjects from cohorts 1 through 9 have completed the study or early terminated. The administrative interim analyses will evaluate all available data at the time of the snapshot. The snapshot will be triggered by the completion of each cohort(s), if completed around the same time.

CCI [redacted]

CCI [redacted]

CCI
CCI CCI

CCI

CCI

# 7. SAFETY ANALYSES

## 7.1. Adverse Events and Deaths

### 7.1.1. Adverse Event Dictionary

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

### 7.1.2. Adverse Event Severity

Adverse events are graded by the investigator as Grade 1, 2, 3, 4, or 5 according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03. 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 AEs met the definitions of SAE specified in the study protocol. Serious AEs captured and stored in the clinical database will be reconciled with the SAE database from the Gilead Pharmacovigilance and Epidemiology Department 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) 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 study drug
- Any AEs leading to premature discontinuation of 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 study drug, 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 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 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 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 dosing date of study drug, will be considered to be treatment emergent. 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 study drug will be considered treatment emergent.

### 7.1.6. Summaries of Adverse Events and Deaths

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

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

- All TEAEs
- TEAEs of Grade 2 or higher
- TEAEs of Grade 3 or higher (by maximum severity)
- All TE treatment-related AEs
- TE Treatment-related AEs of Grade 2 or higher
- TE Treatment-related AEs of Grade 3 or higher (by maximum severity)
- All TE SAEs
- All TE treatment-related SAEs
- All TEAEs leading to premature discontinuation of study drug

- All TEAEs leading to premature discontinuation of study
- All TEAEs leading to dose interruption of study drug

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

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 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 will be summarized by PT only, in order of descending incidence within the pooled treatment groups for:

- All AEs
- TEAEs of Grade 3 or higher
- All treatment-related AEs
- All SAEs
- All TEAEs leading to premature discontinuation of study drug
- All TEAEs leading to premature discontinuation of study
- All TEAEs leading to interruption of study drug

In addition, data listings will be provided for the following (with a variable indicating whether the event is treatment emergent):

- All AEs
- AEs of Grade 3 or higher
- SAEs
- Deaths
- AEs leading to premature discontinuation of study drug
- AEs leading to premature discontinuation of study

## 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 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. 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 CTCAE version 4.03 will be flagged in the data listings, as appropriate.

No formal statistical testing is planned.

### 7.2.1. Summaries of Numeric Laboratory Results

Descriptive statistics will be provided by treatment group for CCI [redacted], creatinine, fasting glucose, fasting insulin, WBC, neutrophils, lymphocytes, hemoglobin, platelets, INR and estimated glomerular filtration rate (eGFR) using the Cockcroft-Gault equation, as follows:

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

Median (Q1, Q3) of the observed values for CCI [redacted], CCI [redacted] CCI creatinine, fasting glucose, fasting insulin, CCI [redacted], CCI WBC, neutrophils, lymphocytes, hemoglobin, platelets, INR, and eGFR, will be plotted using a line plot by treatment group and visit.

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 4.03 will be used for assigning 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.

#### 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. 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 treatment emergent.

#### 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. If the relevant baseline laboratory value is missing, any Grade 3 or 4 values observed within the timeframe specified above will be considered treatment-emergent 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 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 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 dosing date.

A by-subject listing of treatment-emergent Grade 3 or 4 laboratory abnormalities will be provided by subject ID number and visit in chronological order. This listing will include all test

results that were collected throughout the study for the lab test of interest, with all applicable severity grades displayed.

### 7.2.3. Liver-related Laboratory Evaluations

Liver-related abnormalities after initial study drug dosing will be examined and summarized for separately for subjects who meet the criteria for close observation and for subjects who meet the criteria for drug withheld.

#### 7.2.3.1. Criteria for Close Observation

The number and percentage will be summarized according to different baseline CCI level:

- Normal
- Elevated (≥ ULN)

For subjects with normal baseline CCI, close observation is considered if any of the following criteria is met postbaseline:

- CCI
- CCI
- CCI
  - INR > 1.5 (except for subjects on anticoagulant therapy)

For subjects with baseline CCI between 1 and 5 × ULN, close observation is considered if any of the following criteria is met postbaseline:

- CCI
- CCI
- CCI
  - INR > 1.5 (except for subjects on anticoagulant therapy)

CCI

[redacted]

[redacted]

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 of study drug. Number and percentage of subjects who were reported to 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 endpoints of CCI total bilirubin, and INR, 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 nonmissing postbaseline on-treatment values of all relevant tests at the same postbaseline visit date.

Listings of subjects who met the criteria for close observation and who meet the criteria for drug withheld will be provided.

## 7.3. CCI Height, and Vital Signs

Descriptive statistics will be provided by treatment group for CCI, height, BMI and vital signs 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 study drug. Change from baseline to a postbaseline visit will be defined as the postbaseline value minus the baseline value. CCI and vital signs measured at unscheduled visits will be included for the baseline value selection.

Median (Q1, Q3) of the observed values for CCI will be plotted by treatment group and visit.

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. High or low values for vital signs will be flagged. CCI, height, and BMI will be listed separately.

## 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 dosing date of study drug will be included in the prior medication summary regardless of the stop date. 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. 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 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 dosing date of study drug and continued after the first dosing date, or started after the first dosing date but prior to or on the last dosing date of study drug will be considered concomitant medications. Medications started and stopped on the same day as the first dosing date or the last dosing date of study drug will also be considered concomitant. Medications with a stop date prior to the date of first dosing date of study drug or a start date after the last dosing date of 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

A shift table of the investigators' assessment of ECG results at each visit 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.

[redacted]

# 9. REFERENCES

Clopper CJ, Pearson ES. The Use of Confidence or Fiducial Limits Illustrated in the Case of the Binomial. Dec. Biometrika 1934;26 (4):pp. 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. Study Procedures Tables for GS-US-384-3914 (Cohorts 1-9)

| | | Pretreatment Period | | Enrollment | | Treatment Period | | | | | | | | | | End of Treatment | | Follow Up |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Kinetic Biomarkers Cycle 1 | | | | | Kinetic Biomarkers Cycle 2 | | | | | | Kinetic Biomarkers Cycle 3 | | | | | |
| | Screen[a] | Day-14 | Day -11 (±1d) | Day -7 (±1d) | Day 1[b] | Day 7 (WK1) (±3d) | Day 14 (WK2) (±1d) | Day 17 (±1d) | Day 21 (WK3) (±1d) | Day 28 (WK4) (±3d) | Day 35 (WK5) (±3d) | Day 56 (WK8) (±3d) | Day 70 (WK10) (±1d) | Day 73 (±1d) | Day 77 (WK11) (±1d) | Day 84 (WK12) (±3d) | Day 91 (WK13) (±3d) | Day 112 (WK16) (±5d) |
| **Clinical Assessments** | | | | | | | | | | | | | | | | | | |
| Informed Consent | X | | | | | | | | | | | | | | | | | |
| Determine Eligibility[c] | X | X | | | X | | | | | | | | | | | | | |
| Medical History | X | | | | X | | | | | | | | | | | | | |
| Assess ascites and hepatic encephalopathy[d] | X | | | | | | | | | | | | | | | | | |
| Physical Examination | X | | | | X[e] | X[e] | | | | X[e] | | X[e] | | | | X[e] | | X[e] |
| Vital Signs | X | | | | X | X | | | | X | | X | | | | X | | X |
| Height | X | | | | | | | | | | | | | | | | | |
| CCI | | | | | | | | | | | | | | | | | | |
| 12- lead ECG | X | | | | | | | | | | | | | | | X | | |
| CCI | | | | | | | | | | | | | | | | | | |
| MRE, MRI-PDFF | X[g] | | | | | | | | | X | | | | | | X | | |
| Adverse Events | X | X | X | X | X | X | X | X | X | X | | X | X | X | X | X | | X |
| Concomitant Medications | X | X | X | X | X | X | X | X | X | X | | X | X | X | X | X | | X |
| Dispense Study Drug | | | | | X | | | | | X | | X | | | | | | |

| | | Pretreatment Period | | Enrollment | | Treatment Period | | | | | | | | End of Treatment | | | Follow Up |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Kinetic Biomarkers Cycle 1 | | | | | Kinetic Biomarkers Cycle 2 | | | | | | Kinetic Biomarkers Cycle 3 | | | | |
| | Screen[a] | Day-14 | Day -11 (±1d) | Day -7 (±1d) | Day 1[b] | Day 7 (WK1) (±3d) | Day 14 (WK2) (±1d) | Day 17 (±1d) | Day 21 (WK3) (±1d) | Day 28 (WK4) (±3d) | Day 35 (WK5) (±3d) | Day 56 (WK8) (±3d) | Day 70 (WK10) (±1d) | Day 73 (±1d) | Day 77 (WK11) (±1d) | Day 84 (WK12) (±3d) | Day 91 (WK13) (±3d) | Day 112 (WK16) (±5d) |
| Dispense Deuterated Water | | X | | | | | X | | | | | | X | | | | | |
| **Laboratory Assessments** | | | | | | | | | | | | | | | | | | |
| Chemistry | X | | | | X | X | | | | X | | X | | | | X | | X |
| Hematology | X | | | | X | X | | | | X | | X | | | | X | | X |
| Coagulation Panel | X | | | | X | X | | | | X | | X | | | | X | | X |
| Pregnancy Test[h] | X | | | | X | | | | | X | | X | | | | X | | X |
| ApoA1, ApoB, CCI , NMR Lipoprofile | | | | | X | X | | | | X | | X | | | | X | | |
| CCI CCI beta-hydroxybutyrate | | | | | X | | | | | X | | | | | | X | | |
| CCI | | | | | | | | | | | | | | | | | | |
| Lipidomics | | | | | X | | | | | X | | | | | | X | | |
| CCI | | | | | | | | | | | | | | | | | | |
| FGF19, C4 | | | | | X | X | | | | X | | X | | | | X | | |
| CCI | | | | | | | | | | | | | | | | | | |
| Hemoglobin A1c | | | | | X | | | | | | | | | | | X | | |

| | | Pretreatment Period | | Enrollment | | Treatment Period | | | | | | | End of Treatment | | | | | Follow Up |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Kinetic Biomarkers Cycle 1 | | | | | Kinetic Biomarkers Cycle 2 | | | | | | Kinetic Biomarkers Cycle 3 | | | | | |
| | Screen[a] | Day-14 | Day -11 (±1d) | Day -7 (±1d) | Day 1[b] | Day 7 (WK1) (±3d) | Day 14 (WK2) (±1d) | Day 17 (±1d) | Day 21 (WK3) (±1d) | Day 28 (WK4) (±3d) | Day 35 (WK5) (±3d) | Day 56 (WK8) (±3d) | Day 70 (WK10) (±1d) | Day 73 (±1d) | Day 77 (WK11) (±1d) | Day 84 (WK12) (±3d) | Day 91 (WK13) (±3d) | Day 112 (WK16) (±5d) |
| Urine Drug Screening | X | | | | | | | | | | | | | | | | | |
| HIV-1, HBV & HCV Serology | X | | | | | | | | | | | | | | | | | |
| CCI | | | | | | | | | | | | | | | | | | |
| CCI | | | | | | | | | | | | | | | | | | |
| Genomic Sample[l] | | | | | X | | | | | | | | | | | | | |
| CCI | | | | | | | | | | | | | | | | | | |
| Urine Collection for Kinetic Biomarkers | | X | X | X | X | X[m] | X | X | X | X | | X[m] | X | X | X | X | | |
| Blood Collection for Kinetic Biomarkers | | X | X | X | X | X[m] | X | X | X | X | | X[m] | X | X | X | X | | |
| Saliva Collection for Kinetic Biomarkers[n] | | | | | | X | | | | | X[k] | | | | | | X[k] | |

a Screening assessments to be completed within 6 weeks prior to Day -14 visit. The screening period also may be extended under special circumstances with the explicit approval of Gilead Sciences.
b Day 1 assessments must be performed prior to dosing.
c Includes review of historical liver biopsy, obtained within 12 months of Screening (date of initial informed consent) for subjects with bridging fibrosis (F3) and within the last 12 months for subjects with cirrhosis (F4), to assess subject eligibility.
d Assess presence and severity of ascites and hepatic encephalopathy for CPT score (for Cohorts 7 and 8 only).
e Symptom driven physical examination.
CCI

[redacted]

h Females of childbearing potential only: Serum pregnancy testing at screening, urine pregnancy testing will occur at Day 1 and every 4 weeks during the dosing period and for 30 days following the last dose of study drug.

[redacted]

k To be collected at home and provided to the site at the next visit.
l Genomic Sample collected for subjects who have not opted out of sample collection. No additional blood will be drawn.
m Predose Kinetic Biomarkers (for Cohorts 4-9) and 2 hour (± 1 hour) postdose Kinetic Biomarkers (for Cohorts 5, 6, 7 and 9).
n Saliva Collection for Kinetic Biomarkers to be collected for Cohorts 1-3 only.

## Appendix 2. CTCTAE Grade for Laboratory Parameters

| CTCAE v4.03 | CTCAE Grade | | | | |
|---|---|---|---|---|---|
| **Adverse Event** | **1** | **2** | **3** | **4** | **5** |
| CCI | | | | | |
| CCI | | | | | |
| Activated partial thromboplastin time (APTT) prolonged | >ULN - 1.5 x ULN | >1.5 - 2.5 x ULN | >2.5 x ULN; hemorrhage | - | - |
| CCI | | | | | |
| CCI | | | | | |
| Hypercalcemia | Corrected serum calcium of >ULN - 11.5 mg/dL; >ULN - 2.9mmol/L; Ionized calcium >ULN- 1.5 mmol/L | Corrected serum calcium of >11.5 - 12.5 mg/dL; >2.9 - 3.1 mmol/L; Ionized calcium >1.5 -1.6 mmol/L; symptomatic | Corrected serum calcium of >12.5 - 13.5 mg/dL; >3.1 - 3.4 mmol/L; Ionized calcium >1.6 - 1.8 mmol/L; hospitalization indicated | Corrected serum calcium of >13.5 mg/dL; >3.4 mmol/L; Ionized calcium >1.8 mmol/L; life-threatening consequences | Death |
| Hypocalcemia | Corrected serum calcium of <LLN - 8.0 mg/dL; <LLN - 2.0 mmol/L; Ionized calcium <LLN - 1.0 mmol/L | Corrected serum calcium of <8.0 - 7.0 mg/dL; <2.0 - 1.75 mmol/L; Ionized calcium <1.0 - 0.9 mmol/L; symptomatic | Corrected serum calcium of <7.0 - 6.0 mg/dL; <1.75 - 1.5 mmol/L; Ionized calcium <0.9 - 0.8 mmol/L; hospitalization indicated | Corrected serum calcium of <6.0 mg/dL; <1.5 mmol/L; Ionized calcium <0.8 mmol/L; life-threatening consequences | Death |

| CTCAE v4.03 | CTCAE Grade | | | | |
|---|---|---|---|---|---|
| **Adverse Event** | **1** | **2** | **3** | **4** | **5** |
| Chronic kidney disease | eGFR (estimated Glomerular Filtration Rate) or CrCl (creatinine clearance) <LLN – 60 ml/min/1.73 m2 or proteinuria 2+ present; urine protein/creatinine >0.5 | eGFR or CrCl 59 – 30 ml/min/1.73 m2 | eGFR or CrCl 29 – 15 ml/min/1.73 m2 | eGFR or CrCl <15 ml/min/1.73 m2; dialysis or renal transplant indicated | Death |
| Creatinine increased | >1 - 1.5 x baseline; >ULN - 1.5 x ULN | >1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN | >3.0 baseline; >3.0 - 6.0 x ULN | >6.0 x ULN | - |
| Gamma-glutamyl transferase (GGT) increased | >ULN - 2.5 x ULN | >2.5 - 5.0 x ULN | >5.0 - 20.0 x ULN | >20.0 x ULN | - |
| Hyperglycemia | Fasting glucose value >ULN - 160 mg/dL; Fasting glucose value >ULN - 8.9 mmol/L | Fasting glucose value >160 - 250 mg/dL; Fasting glucose value >8.9 - 13.9 mmol/L | >250 - 500 mg/dL; >13.9 - 27.8 mmol/L; hospitalization indicated | >500 mg/dL; >27.8 mmol/L; life-threatening consequences | Death |
| Hypoglycemia | <LLN - 55 mg/dL; <LLN - 3.0 mmol/L | <55 - 40 mg/dL; <3.0 - 2.2 mmol/L | <40 - 30 mg/dL; <2.2 - 1.7 mmol/L | <30 mg/dL; <1.7 mmol/L; life-threatening consequences; seizures | Death |
| Hemoglobin increased | Increase in >0 - 2 gm/dL above ULN or above baseline if baseline is above ULN | Increase in >2 - 4 gm/dL above ULN or above baseline if baseline is above ULN | Increase in >4 gm/dL above ULN or above baseline if baseline is above ULN | - | - |

| CTCAE v4.03 | CTCAE Grade | | | | |
|---|---|---|---|---|---|
| **Adverse Event** | **1** | **2** | **3** | **4** | **5** |
| International normalized ratio (INR) increased | >1 - 1.5 x ULN; >1 - 1.5 times above baseline if on anticoagulation | >1.5 - 2.5 x ULN; >1.5 - 2.5 times above baseline if on anticoagulation | >2.5 x ULN; >2.5 times above baseline if on anticoagulation | - | - |
| Hyperkalemia | >ULN - 5.5 mmol/L | >5.5 - 6.0 mmol/L | >6.0 - 7.0 mmol/L; hospitalization indicated | >7.0 mmol/L; life-threatening consequences | Death |
| Hypokalemia | <LLN - 3.0 mmol/L | <LLN - 3.0 mmol/L; symptomatic; intervention Indicated | <3.0 - 2.5 mmol/L; hospitalization indicated | <2.5 mmol/L; life-threatening consequences | Death |
| Lymphocyte count decreased | <LLN - 800/mm3; <LLN - 0.8 x 10e9 /L | <800 - 500/mm3; <0.8 - 0.5 x 10e9 /L | <500 - 200/mm3; <0.5 - 0.2 x 10e9 /L | <200/mm3; <0.2 x 10e9 /L | - |
| 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 |
| 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 |
| 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 | - |
| Hypophosphatemia | <LLN - 2.5 mg/dL; <LLN - 0.8 mmol/L | <2.5 - 2.0 mg/dL; <0.8 - 0.6 mmol/L | <2.0 - 1.0 mg/dL; <0.6 - 0.3 mmol/L | <1.0 mg/dL; <0.3 mmol/L; life-threatening consequences | Death |
| Platelet count decreased | <LLN - 75,000/mm3; <LLN - 75.0 x 10e9 /L | <75,000 - 50,000/mm3; <75.0 - 50.0 x 10e9 /L | <50,000 - 25,000/mm3; <50.0 - 25.0 x 10e9 /L | <25,000/mm3; <25.0 x 10e9 /L | - |
| Hypernatremia | >ULN - 150 mmol/L | >150 - 155 mmol/L | >155 - 160 mmol/L; hospitalization indicated | >160 mmol/L; life-threatening consequences | Death |
| Hyponatremia | <LLN - 130 mmol/L | - | <130 - 120 mmol/L | <120 mmol/L; life-threatening consequences | Death |

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

Note: Refer to Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03, which can be found at https://evs nci nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

## Appendix 3. Programming Specifications

- MELD score calculation:

MELD score = 3.8 [Ln total bilirubin (mg/dL)] + 11.2 [Ln INR] + 9.6 [Ln creatinine (mg/dL)] + 6.43. Lab values less than 1 are set to 1. Round to integer. The lab parameters need to be measured from the same blood draw.

CCI

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

CCI

[redacted]

- [redacted]
- [redacted]

CCI