# STATISTICAL ANALYSIS PLAN

| | |
|---|---|
| **Study Title:** | A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety and Efficacy of Selonsertib (GS-4997), GS-0976, GS-9674, and Combinations in Subjects with Bridging (F3) Fibrosis or Compensated Cirrhosis (F4) due to Nonalcoholic Steatohepatitis (NASH) |
| **Name of Test Drug:** | Selonsertib (SEL, GS-4997), GS-0976 and GS-9674 |
| **Study Number:** | GS-US-454-4378 |
| **Protocol Version (Date):** | Original: 08 January 2018<br>Amendment 1: 31 January 2018<br>Amendment 2: 22 February 2018<br>Amendment 3: 10 May 2018<br>Amendment 4: 25 April 2019 |
| **Analysis Type:** | Interim and Final |
| **Analysis Plan Version:** | 1.0 |
| **Analysis Plan Date:** | 22 May 2019 |
| **Analysis Plan Author(s):** | PPD<br>PPD |

**CONFIDENTIAL AND PROPRIETARY INFORMATION**

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# LIST OF ABBREVIATIONS

| | |
|---|---|
| AE | adverse event |
| CCI | [redacted] |
| [redacted] | [redacted] |
| ANCOVA | analysis of covariance |
| APRI | AST to platelet ratio index |
| CCI | [redacted] |
| α-SMA | α-smooth muscle actin |
| BLQ | below the limit of quantitation |
| BMI | body mass index |
| CAP | controlled attenuation parameter |
| CI | confidence interval |
| CLDQ | chronic liver disease questionnaire |
| CK-18 | cytokeratin-18 |
| CMH | Cochran-Mantel-Haenszel |
| CCI | [redacted] |
| CRP | C-reactive protein |
| CSR | clinical study report |
| CTCAE | Common Toxicity Criteria for Adverse Events |
| DILI | drug-induced liver injury |
| DMC | data monitoring committee |
| ECG | electrocardiogram |
| eCRF | electronic case report form |
| ET | early termination |
| CCI | [redacted] |
| CCI | [redacted] |
| FIB-4 | fibrosis-4 |
| FU | Follow-up |
| CCI | [redacted] |
| CCI | [redacted] |
| Hgb | hemoglobin |
| HbA1c | hemoglobin A1c |
| HDL | high density lipoprotein |
| HLT | high-level term |
| HOMA-IR | homeostasis model assessment of insulin resistance |
| CCI | [redacted] |
| ID | identification |
| IFG | impaired fasting glucose |
| CCI | [redacted] |
| LDL | low density lipoprotein |

| | |
|---|---|
| LLT | lower-level term |
| LOQ | limit of quantitation |
| MedDRA | medical dictionary for regulatory activities |
| MELD | model for end-stage liver disease |
| MH | Mantel-Haenszel |
| CCI | [redacted] |
| MRI-PDFF | magnetic resonance imaging – proton density fat fraction |
| NAFLD | nonalcoholic fatty liver disease |
| NAS | NAFLD activity score |
| NASH | nonalcoholic steatohepatitis |
| PIIINP | procollagen III N-terminal propeptide |
| PT | preferred term |
| PTM | placebo-to-match |
| QoL | quality of life |
| Q1, Q3 | first quartile, third quartile |
| SAF | steatosis, activity and fibrosis |
| SAP | statistical analysis plan |
| SD | standard deviation |
| SEL | selonsertib |
| SF-36 | Short Form (36) Health Survey |
| SI (units) | international system of units |
| SOC | system organ class |
| TEAE | treatment-emergent adverse event |
| TFLs | tables, figures, and listings |
| TIMP1 | tissue inhibitor of metalloproteinase 1 |
| VLDL | very low density lipoprotein |
| ULN | upper limit of normal |
| WBC | white blood cell count |
| WHO | World Health Organization |
| WPAI | work productivity and activity impairment questionnaire |

# PHARMACOKINETIC ABBREVIATIONS

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

# 1. INTRODUCTION

This statistical analysis plan (SAP) describes the statistical analysis methods and data presentations to be used in tables, figures, and listings (TFLs) in the administrative interim analysis at Week 24 and the final analysis and clinical study report (CSR) at Week 48 for Study GS-US-454-4378. This SAP is based on the study protocol Amendment 4 dated 25 April 2019 and the electronic case report form (eCRF). The SAP will be finalized before interim analysis database finalization. Any changes made after the finalization of the SAP will be documented in the CSR.

## 1.1. Study Objectives

The primary objectives of this study are as follows:

- To assess the safety and tolerability of selonsertib (SEL, GS-4997), GS-0976, and GS-9674, administered alone or in combination, in subjects with bridging fibrosis or compensated cirrhosis due to NASH

- To evaluate changes in liver fibrosis, as measured by the NASH Clinical Research Network (CRN) classification, without worsening of NASH (defined as any increase in hepatocellular ballooning or lobular inflammation)

CCI [redacted]

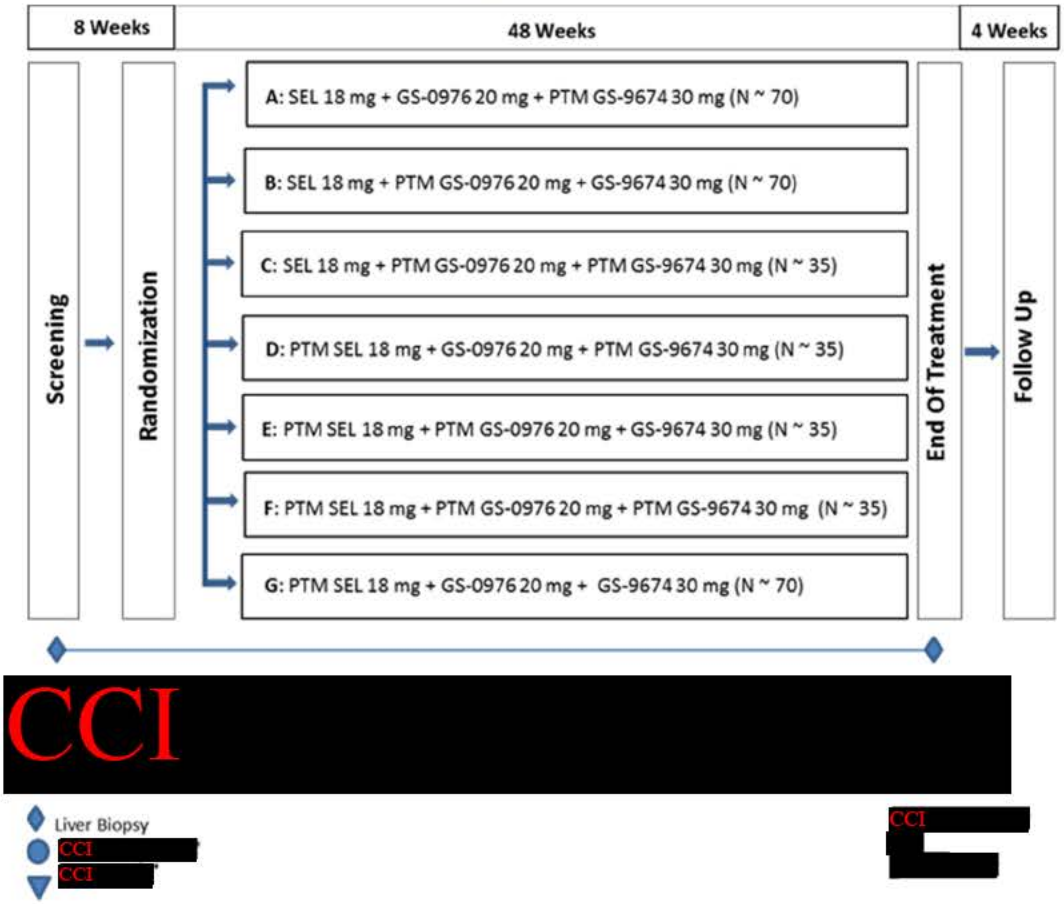
[redacted]

## 1.2. Study Design

This is a Phase 2, randomized, double-blind, placebo-controlled study evaluating the safety and efficacy of SEL, GS-0976, GS-9674, and combinations in subjects with bridging fibrosis or compensated cirrhosis due to NASH.

The overall study design is presented graphically in Figure 1-1. The complete schedule of assessments can be found in Appendix 1.

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




### 1.2.1. Study Treatments

Subjects meeting the study's entry criteria will be assigned randomly in a 2:2:1:1:1:1:2 ratio to 1 of 7 treatment groups (Group A, Group B, Group C, Group D, Group E, Group F, or Group G), with approximately 70 subjects in each combination treatment group and approximately 35 subjects in each single agent or placebo group, as shown in Figure 1-1. Randomization will be stratified by the presence or absence of diabetes mellitus, as determined by medical history or based on the screening lab values if previously undiagnosed (hemoglobin A1c [HbA1c] $\geq$ 6.5% or fasting plasma glucose $\geq$ 126 mg/dL) and by the presence or absence of cirrhosis (F4) as determined by the central biopsy reader at screening.

Study drugs will be administered for a total of 48 weeks from the Day 1 visit. Dosage and administration of the study drugs and reference products are described in the protocol.

Because Study GS-US-384-1943 and GS-US-384-1944 demonstrated lack of efficacy and are discontinued after the Week 48 Interim Analysis, subjects from the SEL monotherapy treatment group (A) will be unblinded and discontinued from the study.

### 1.2.2. Duration of Study

Participation can last up to 60 weeks, which includes an 8-week Screening period, a 48-week On-Treatment period, and a 4-week Follow-Up period.

### 1.2.3. End of Study

End of study is considered to be completion of the Follow-Up visit.

### 1.2.4. Post Study Care

There is no offered post study care.

## 1.3. Sample Size and Power

Due to the exploratory nature of this study, no formal power calculations were used to determine sample size. The number of subjects was chosen based on clinical experience with other similar proof-of-concept studies; however, with a sample size of approximately 70 subjects in each active combination treatment arm and approximately 35 subjects in the placebo arm, the study has over 80% power to detect a difference in the proportion of subjects with a ≥ 1-stage improvement in fibrosis without worsening of NASH of 25% or more at Week 48 at a significance level of 0.05 (two-sided), assuming the proportion of subjects that meet the endpoint in the placebo arm is 7.2%.

# 2. TYPE OF PLANNED ANALYSIS

## 2.1. Interim Analyses

### 2.1.1. DMC Interim Analyses

An external multidisciplinary Data Monitoring Committee (DMC) will review the progress of the study and perform interim reviews of the safety data in order to protect subject welfare and preserve study integrity. To ensure the best interests of the participants, the DMC will recommend to the sponsor if 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 35 subjects (approximately 5 per treatment group) have completed assessments through Week 4. Additional meetings will be scheduled approximately every 6 months.

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

While the DMC will be asked to advise Gilead regarding future conduct of the study, including possible early study termination, or discontinuation of select treatment group, Gilead retains final decision-making authority on all aspects of the study.

### 2.1.2. Week 24 Analysis

An administrative interim analysis will be performed after all randomized subjects have completed Week 24 assessments or prematurely discontinued the study.

## 2.2. Final Analysis

After all subjects have completed the study, outstanding data queries have been resolved or adjudicated as unresolvable, and the data have been cleaned and finalized, the study blind will be broken and 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.

All statistical tests will be 2-sided and performed at the 5% significance level unless otherwise specified.

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

## 3.1. Analysis Sets

Analysis sets define the subjects to be included in an analysis. Analysis sets and their definitions are provided in this section. Subjects included in each analysis set will be determined before the study blind is broken for analysis. 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 Randomized Analysis Set

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 subjects who took at least 1 dose of study drug and were randomized into the study. 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.

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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 randomized. For analyses based on the Safety Analysis Set, subjects will be grouped according to the actual treatment received. The actual treatment received will differ from the randomized treatment only when their actual treatment differs from randomized treatment for the entire treatment duration.

For the PK Analysis Set, subjects will be grouped according to the actual treatment they received.

### 3.3. Strata and Covariates

Subjects will be randomly assigned to treatment groups via the interactive voice or web response system (IXRS) using a stratified randomization schedule. Stratification will be based on the following variables:

- Presence or absence of diabetes mellitus as determined by medical history or based on the screening laboratory values if previously undiagnosed (HbA1c $\geq$ 6.5% or fasting plasma glucose $\geq$ 126 mg/dL)
- Presence or absence of cirrhosis (F4 vs. Non-F4) as determined by the central biopsy reader at screening

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.

Efficacy endpoints will be evaluated using the presence or absence of diabetes mellitus at baseline, and the presence or absence of cirrhosis at baseline, as stratification factors for analyses, as specified in Section 6.

For efficacy endpoints, the baseline value of the efficacy variable(s) will be included as a covariate in the efficacy analysis model, as appropriate.

### 3.4. Examination of Subject Subgroups

Subgrouping of subjects based on the randomization stratification factors of presence or absence of diabetes mellitus and cirrhosis at baseline will be explored for subgroup analyses.

The primary efficacy endpoint(s) will be examined using the following subgroups:

- Subjects with diabetes mellitus at baseline;
- Subjects without diabetes mellitus at baseline;
- Subjects with cirrhosis (F4) at baseline;
- Subjects without cirrhosis (Non-F4) at baseline;

For the comparison of treatment difference between 2 treatment groups in each subgroup, only the point estimate and 95% confidence interval (CI) will be presented.

## 3.5. Multiple Comparisons

All efficacy endpoints are exploratory in nature and may be tested using 2-sided tests at the 5% significance level without multiplicity adjustment.

## 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. Exceptions are presented in this document.

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

### 3.6.2. 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

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 (in years) on the date of the first dose of study drug will be used for analyses and presentation 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 an enrolled subject was not dosed with any study drug, the randomization 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. 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).

CCI [redacted]

Natural logarithm transformation will be used for plasma/blood concentrations and analysis of PK parameters. Plasma concentration values that are below the limit of quantitation (BLQ) will be presented as "BLQ" in the concentration data listing. Values that are BLQ will be treated as 0 at predose time points, and one-half the value of the LOQ at postbaseline time points.

The following conventions will be used for the presentation of summary and order statistics:

- If at least 1 subject has a concentration value of BLQ for the time point, the minimum value will be displayed as "BLQ."
- If more than 25% of the subjects have a concentration data value of BLQ for a given time point, the minimum and Q1 values will be displayed as "BLQ."
- If more than 50% of the subjects have a concentration data value of BLQ for a given time point, the minimum, Q1, and median values will be displayed as "BLQ."

- If more than 75% of the subjects have a concentration data value of BLQ for a given time point, the minimum, Q1, median, and Q3 values will be displayed as "BLQ."
- If all subjects have concentration data values of BLQ for a given time point, all order statistics (minimum, Q1, median, Q3, and maximum) will be displayed as "BLQ."

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## 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 predose study days: 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.

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Selected safety and efficacy data, unless otherwise specified, 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 Follow-Up (FU).

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The analysis windows for select measures are provided in Table 3-1 to Table 3-5.

**Table 3-1. Analysis Visit Windows for Chemistry, Hematology, Coagulation, CCI [redacted], Glucose, Vital Signs, and Body Weight**

| Nominal Visit | Nominal Study Day | Lower Limit | Upper Limit |
|---|---|---|---|
| Baseline | 1 | (none) | 1 |
| Week 1 | 8 | 2 | 18 |
| Week 4 | 29 | 19 | 42 |
| Week 8 | 57 | 43 | 70 |
| Week 12 | 85 | 71 | 98 |
| Week 16 | 113 | 99 | 126 |
| Week 20 | 141 | 127 | 154 |
| Week 24 | 169 | 155 | 182 |
| Week 28 | 197 | 183 | 210 |
| Week 32 | 225 | 211 | 238 |
| Week 36 | 253 | 239 | 266 |
| Week 40 | 281 | 267 | 294 |
| Week 44 | 309 | 295 | 322 |
| Week 48 | 337 | 323 | ≥337 |

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**Table 3-5. Analysis Visit Windows for Biopsy Data and electrocardiogram (ECG)**

| Nominal Visit | Nominal Study Day | Lower Limit | Upper Limit |
|---|---|---|---|
| Baseline | 1 | (none) | 1 |
| Week 48 | 337 | 2 | ≥337 |

Data relating to unscheduled visits and early termination (ET) visits may be assigned to a particular visit or time point 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 (including ET FU visit) will be summarized as a separate visit, and labeled “Follow-up Visit”

### 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 dosing date of 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.

[redacted]

- For postbaseline values:

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

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

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

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

Postbaseline histology endpoints will be selected in each visit window according to the following rules:

- Histology endpoints will be derived based on parameters collected from one biopsy sampling date if all parameters needed are available.

- When multiple values of an endpoint are derived from biopsy samples obtained on different dates in one visit window, the value closest to the nominal day will be chosen for analysis. When two values are equidistant from the nominal day, the later value will be selected.

- When an endpoint cannot be derived due to missing parameter(s) from one biopsy sampling date, histology parameters from different biopsy sampling dates in that visit window will be used to derive the endpoint. Nonmissing value of each individual parameter closest to the nominal day for that visit window will be selected. When two records are equidistant from the nominal day, the later record will be selected.

- When an endpoint cannot be derived based on all biopsy samples in a visit window, the histology endpoint will be considered missing.

# 4. SUBJECT DISPOSITION

## 4.1. Subject Enrollment and Disposition

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

A similar enrollment table will be provided by randomization stratum. The denominator for the percentage of subjects in the stratum will be the total number of enrolled 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. This summary will present the number of subjects screened, the number of subjects randomized, and the number of subjects in each of the categories listed below:

- Safety Analysis Set
- Full Analysis Set
- Pharmacokinetic Analysis Set (final analysis only)
- [redacted]
- Continuing study drug (Week 24 analysis only)
- Completed study drug
- Did not complete study drug with reasons for premature discontinuation of study drug
- Continuing study (Week 24 analysis only)
- 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 bottle ID

### 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 and divided by 7, 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 for subjects included in the final analyses or the last available date in the database snapshot for subjects who were still on treatment at the time of an interim analysis..

The total duration of exposure to study drug will be summarized using descriptive statistics and using the number (ie, cumulative counts) and percentage of subjects exposed through the following time periods: 1 day, 4 weeks, 8 weeks, 12 weeks, 16 weeks, 20 weeks, 24 weeks, 36 weeks and 48 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 total number of tablets administered will be summarized using descriptive statistics.

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

$$\text{Total Number of Tablets Administered} = \sum \text{No. of Tablets Dispensed} - \sum \text{No. of Tablets Returned}$$

When calculating total number of tablets administered according to the formula above, for subjects in the active drug monotherapy and combination therapy groups, number of tablets of the active drugs will be included, and the placebo-to-match (PTM) tablets are not counted; all tablets will be counted when calculating total number of tablets administered for subjects in the placebo group.

The level of on-treatment 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 expected to be administered during a subject's actual on-treatment period based on the study drug regimen.

The level of on-treatment adherence will be expressed as a percentage using the following formula:

$$\text{On-Treatment Adherence (\%)} = \left( \frac{\text{Total Amount of Study Drug Administered}}{\text{Study Drug Expected to be Administered on Treatment}} \right) \text{x } 100$$

For each subject, the total number of days on treatment is calculated as the last dosing date minus first dosing date plus 1. For subjects in the placebo group, total number of study drug expected to be administered will be equal to the number of days on treatment multiplied by 3. For subjects on SEL/GS-0976/GS-9674 monotherapy groups, total number of study drug expected to be administered will be the same as number of days on treatment. For subjects on combinations, total number of study drug expected to be administered will be the number of days on treatment multiplies by 2.

At interim analyses, if the subject is ongoing, the number of tablets administered and expected to be administered on treatment will be calculated based on study drug accountability data.

Descriptive statistics for the level of on-treatment adherence with the number and percentage of subjects belonging to adherence categories (eg, $< 75\%$, $\geq 75$ to $< 90\%$, $\geq 90\%$) will be provided by treatment group for the Safety Analysis Set. No formal statistical testing is planned.

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

### 4.3. Protocol Deviations

Subjects who did not meet the eligibility criteria for study entry, but enrolled in the study will be summarized regardless of whether they were exempted by the sponsor or not. The summary will present the number and percentage of subjects who did not meet at least 1 eligibility criterion 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) 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. Baseline Characteristics

Baseline characteristics include:

- Body weight (in kg),
- Height (in cm),
- Body mass index (BMI; in $kg/m^2$),
- BMI category (< 18 $kg/m^2$ [if applicable], 18 to < 25 $kg/m^2$, 25 to < 30 $kg/m^2$, and ≥ 30 $kg/m^2$),
- [redacted]
- [redacted]
- Diabetes mellitus (absence or presence),
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- HOMA-IR,
- HbA1c (%),
- [redacted]
- [redacted]

- [redacted]
- [redacted]
- Platelets ($\times 10^3$ /uL),
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- AST to platelet ratio index (APRI),
- Fibrosis-4 (FIB-4),
- Ishak fibrosis stage,
- NASH CRN fibrosis stage,
- Cirrhosis status (cirrhotic or non-cirrhotic),
- Hepatic collagen content (%),
- α-smooth muscle actin (α-SMA) (%)
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- Lobular inflammation grade,
- Hepatocellular ballooning grade,

[redacted]

- Enrolled based on non-invasive criteria,
- Smoking Status.

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.

CCI [redacted]

### 5.3. Medical History

General medical history data will be collected at screening. General medical history data will be coded using the current version of medical dictionary for regulatory activities (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 medical history dataset.

General medical history data will be listed.

# 6. EFFICACY ANALYSES

All efficacy analyses are exploratory.

## 6.1. Histology Response Efficacy Endpoints

### 6.1.1. Definition of Histology Response Efficacy Endpoints

The histology efficacy endpoints include:

1) The proportion of subjects who achieve a ≥ 1-stage improvement in fibrosis (according to the NASH CRN classification) without worsening of NASH (defined as a ≥ 1-point increase in hepatocellular ballooning or lobular inflammation) at Week 48;
2) Proportion of subjects who have a ≥ 1-stage improvement in fibrosis (according to the NASH CRN classification) at Week 48;
3) Proportion of subjects who have NASH resolution (defined as lobular inflammation of 0 or 1 from at least 1 at baseline and hepatocellular ballooning reduced to 0 from at least 1 at baseline; both criteria are necessary conditions) without worsening of fibrosis at Week 48;
4) Proportion of subjects with bridging fibrosis (F3) or less at baseline who progress to cirrhosis (F4) at Week 48;
5) Proportion of subjects with at least 1-point improvement in NAS elements, and those with at least 2-point improvement in NAS at Week 48.

### 6.1.2. Analysis of Histology Response Efficacy Endpoint

The 95% CI for proportion of subjects who met the endpoint in each treatment group based on the Clopper-Pearson method will be calculated.

A stratified Mantel-Haenszel (MH) test will be used to compare the differences in proportions of subjects who met the endpoint between each active arm (SEL, GS-0976, GS-9674, SEL + GS-0976, SEL + GS-9674, GS-0976 + GS-9674) and placebo, adjusting for presence or absence of cirrhosis and diabetes mellitus at baseline. The p-value and 95% CI of the difference in proportions between each active arm and placebo will be constructed based on stratum-adjusted MH proportions as follows {Koch 1989}:

$$p_A - p_B \pm Z_{(1-\alpha/2)} * SE(p_A - p_B),$$

where

- $(p_A - p_B) = \frac{\sum w_h d_h}{\sum w_h}$, is the stratum-adjusted MH proportion difference, where $d_h = p_{Ah} - p_{Bh}$ is the difference in the proportion of subjects who met the endpoint between SEL (GS-0976, GS-9674, SEL + GS-0976, SEL + GS-9674, GS-0976 + GS-9674) and placebo in stratum h.

- $w_h = \frac{n_{Ah} n_{Bh}}{n_{Ah} + n_{Bh}}$, is the weight based on the harmonic mean of sample size per treatment group for each stratum where $n_{Ah}$ and $n_{Bh}$ are the sample sizes of SEL (GS-0976, GS-9674, SEL + GS-0976, SEL + GS-9674, GS-0976 + GS-9674) and placebo in stratum h.
- $SE(p_A - p_B) = \sqrt{\frac{\sum w \left[ \frac{p^*_{Ah}(1-p^*_{Ah})}{n_{Ah}-1} + \frac{p^*_{Bh}(1-p^*_{Bh})}{n_{Bh}-1} \right]}{(\sum w_h)^2}}$, where
- $p^*_{Ah} = \frac{m_{Ah} + 0.5}{n_{Ah} + 1}$ and $p^*_{Bh} = \frac{m_{Bh} + 0.5}{n_{Bh} + 1}$, and
- $m_{Ah}$ and $m_{Bh}$ are the number of subjects who met the endpoint in SEL (GS-0976, GS-9674, SEL + GS-0976, SEL + GS-9674, GS-0976 + GS-9674) and placebo in stratum h.
- $\alpha = 0.05$ for the calculation of 95% CI
- $Z_{(1-\alpha/2)} = Z_{0.975}$ is the 97.5th percentile of the normal distribution
- Z score = $\frac{(p_A - p_B)}{SE_{(p_A - p_B)}}$

If the computed lower confidence bound is less than –1, the lower bound is defined as –1. If the computed upper confidence bound is greater than 1, then the upper bound is defined as 1.

The point estimates, 95% CIs, and corresponding p-values based on Z test for the differences in proportions between each active arm and placebo will be calculated. Additionally, point estimates, 95% CIs, and p-values for the difference in proportions between combination groups and the mono treatment groups forming the combination will be also calculated.

Subjects missing data regarding fibrosis stage or NAS elements used to define worsening of NASH (hepatocellular ballooning and lobular inflammation) at Week 48 will be excluded from the analysis. For NASH resolution, subjects with baseline lobular inflammation and hepatocellular ballooning grades of 1 or above, and who had change in fibrosis available (for baseline non-F4 subjects) or who had baseline fibrosis stage of F4 are included. For the analysis of subjects progressed to cirrhosis, only subjects with non-F4 CRN fibrosis stage at baseline are to be included.

Forest plots of the treatment differences in proportion of subjects who met each histology endpoint will be generated for the subgroup analyses as described in Section 3.4

### 6.1.3. Sensitivity Analysis of Histology Response Efficacy Endpoints

The histology response efficacy endpoints defined in Section 6.1.1 will also be analyzed on the FAS Analysis Set excluding subjects from sites with major compliance issues, as sensitivity analysis.

CCI [redacted]

CCI

[redacted]

CCI

[redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

## 6.3. Change From Protocol-Specified Efficacy Analyses

CCI [redacted]

A few subjects were enrolled into the study with baseline fibrosis stage F0 – F2. In the description of subgroups, and the planned analyses for F3 subjects, "F3" subjects were replaced by "non-F4" subjects, to include the F0 – F2 subjects together with the F3 subjects.

# 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. The AE dataset will provide SOC, HLGT, HLT, PT, and LLT.

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

### 7.1.4. Serious Adverse Events

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

### 7.1.5. Treatment-Emergent Adverse Events

7.1.5.1. Definition of Treatment-Emergent Adverse Events

Treatment-emergent adverse events (TEAEs) 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.

#### 7.1.5.2. 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, HLT, PT, and treatment group. For other AEs described below, summaries will be provided by SOC, PT, and treatment group:

- TEAEs by severity grade
- TEAEs of Grade 3 or higher (by maximum severity)
- TEAEs of Grade 2 or higher
- All TE treatment-related AEs
- TE Treatment-related AEs of Grade 3 or higher (by maximum severity)
- TE Treatment-related AEs of Grade 2 or higher
- All TE treatment-related AEs by severity grade
- All TE SAEs
- All TE treatment-related SAEs
- All TEAEs leading to premature discontinuation of study drug
- All TEAEs leading to death (ie, outcome of death)
- All TEAEs leading to temporary 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 also be 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 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, all TEAEs, TE SAEs and TE treatment-related AEs, TE treatment-related SAEs will be summarized by PT only, in descending order of total frequency.

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

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

CCI [redacted]

## 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.

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 urinalysis 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

Descriptive statistics will be provided by treatment group for creatinine, creatinine clearance (Cockroft-Gault), white blood cells (WBC), neutrophils, lymphocytes, hemoglobin, platelets, and free fatty acid 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

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 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. 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.

Treatment-emergent laboratory abnormalities are defined as values within the reference range at baseline, but which become lower or higher than the reference range 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. If the relevant baseline laboratory value is missing, any postbaseline laboratory value that is lower or higher than the reference range 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 for subjects who permanently discontinued study drug or the last available date in the database snapshot for subjects who were still on treatment at the time of an interim analysis. If the relevant baseline laboratory value is missing, any Grade 3 or 4 values observed within the timeframe specified above 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 abnormal flags displayed.

### 7.2.3. Liver-related Laboratory Evaluations

Subjects will be grouped according to their baseline ALT/AST level; ≤ upper limit of reference range (ULN) or > ULN, respectively. Liver-related abnormalities after initial study drug dosing will be examined and summarized using the number and percentage of subjects who were reported to have the following laboratory test values for postbaseline measurements:

For subjects with ALT/AST ≤ ULN

- Subjects meeting criteria for close observation
  - ALT/AST > 3 × ULN
- Subjects meeting criteria for study drug withheld
  - ALT/AST > 8 × ULN
  - ALT/AST > 5 × ULN for 2 weeks
  - ALT/AST > 3 × ULN and total bilirubin > 2 × ULN
  - ALT/AST > 3 × ULN and direct bilirubin > 2 × Baseline (in subjects with Gilbert's syndrome)
  - ALT/AST > 3 × ULN and INR > 1.5 (if not on anticoagulation)

For subjects with ALT/AST > ULN

- Subjects meeting criteria for close observation
  - ALT/AST > 2 × Baseline
  - ALT/AST > 300 U/L
- Subjects meeting criteria for study drug withheld
  - ALT/AST > 8 × Baseline
  - ALT/AST > 500 U/L
  - ALT/AST > 3 × Baseline and total bilirubin > 2 × ULN
  - ALT/AST > 3 × Baseline and direct bilirubin > 2 x Baseline (in subjects with Gilbert's syndrome)
  - ALT/AST > 300 U/L, and total bilirubin > 2 × ULN
  - ALT/AST > 300 U/L, and direct bilirubin > 2 x Baseline (in subjects with Gilbert's syndrome)
  - ALT/AST > 3 × Baseline and INR > 1.5 (if not on anticoagulation)
  - ALT/AST > 300 U/L and INR > 1.5 (if not on anticoagulation)

The summary will include data from all postbaseline visits up to 30 days after the last dose of study drug. For individual laboratory tests, subjects will be counted once based on the most severe postbaseline values. For both the composite endpoint of AST or ALT and total or direct bilirubin, 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 values 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. Vital Signs

Descriptive statistics will be provided by treatment group for vital signs (Systolic Blood Pressure [mmHg], Diastolic Blood Pressure [mmHg], Respiratory Rate [breaths/min], Pulse Rate [beats/min], Temperature [°C]) 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. 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, CCI [redacted] will be provided 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 medications 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 when the stop date is. If a partial start date is entered the medication will be considered prior unless the month and year (if day is missing) or year (if day and month are missing) of the start date are after the first dosing date. 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 medications with a start date prior to or on the first dosing date of study drug and continued to be taken 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

### 7.5.1. Investigator Electrocardiogram Assessment

A shift table of the investigators' assessment of ECG results at postbaseline 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. Other Safety Measures

No additional safety measures are specified in the protocol.

### 7.7. Changes From Protocol-Specified Safety Analyses

In addition to the protocol-specified analyses as described in Section 7.1 through 7.6, select safety endpoints will be analyzed in the Safety Analysis Set excluding subjects from sites with major compliance issues.

[redacted]


CCI

CCI [redacted]

CCI [redacted]

[redacted]

CCI [redacted]

[redacted]

CCI [redacted]

# 9. REFERENCES

Elman S, Hynan LS, Gabriel V, Mayo MJ. The 5-D itch scale: a new measure of pruritus. Br J Dermatol 2010;162 (3):587-93.

Koch GG, Carr GJ, Amara IA, Stokes ME, Uryniak TJ. Categorical Data Analysis. Chapter 13 in Berry, D.A. (ed.). Statistical Methodology in the Pharmaceutical Sciences. New York: Marcel Dekker, Inc., 1989:pp. 414-21.

# 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
Appendix 2. CTCAE Grade for Laboratory Parameters
CCI [redacted]
Appendix 4. Liver Function Prognostic Score Calculations
CCI [redacted]
CCI [redacted]
CCI [redacted]

## Appendix 1. Schedule of Assessments

| Assessments | Screening | Day 1 | On-Treatment Visits | | | | | | | | | | | | | ET | Follow-Up |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Week 1 | Week 4 | Week 8 | Week 12 | Week 16 | Week 20 | Week 24 | Week 28 | Week 32 | Week 36 | Week 40 | Week 44 | Week 48 | | |
| **Clinical Assessments** | | | | | | | | | | | | | | | | | |
| Written Informed Consent | X | | | | | | | | | | | | | | | | |
| Determine Eligibility | X | X | | | | | | | | | | | | | | | |
| Medical History | X | | | | | | | | | | | | | | | | |
| Physical Examination | X[a] | X | X | X | X | X | X | X | X[a] | X | X | X | X | X | X[a] | X[a] | X |
| Vital Signs including Body Weight | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Height | X | | | | | | | | | | | | | | | | |
| CCI | | | | | | | | | | | | | | | | | |
| 12-lead ECG | X | | | | | | | | | | | | | | X | X | X |
| CCI | | | | | | | | | | | | | | | | | |
| Assess Ascites and HE | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| Abdominal Ultrasound | X[b] | | | | | | | | X | | | | | | X | X | |
| CCI | | | | | | | | | | | | | | | | | |
| Liver Biopsy | X[e] | | | | | | | | | | | | | | X | X[d] | |
| CCI | | | | | | | | | | | | | | | | | |
| CCI | | | | | | | | | | | | | | | | | |

| Assessments | Screening | Day 1 | On-Treatment Visits | | | | | | | | | | | | | ET | Follow-Up |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Week 1 | Week 4 | Week 8 | Week 12 | Week 16 | Week 20 | Week 24 | Week 28 | Week 32 | Week 36 | Week 40 | Week 44 | Week 48 | | |
| Lifestyle Questionnaire | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| Lifestyle Modification Counseling | | X | | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| Dispense Study Drugs | | X | | X | X | X | X | X | X | X | X | X | X | X | | | |
| Review of Study Drug Dosing Compliance (Pill Count) | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| Concomitant Medications | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Adverse Events | X[i] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| **Laboratory Assessments** | | | | | | | | | | | | | | | | | |
| Chemistry, Hematology, Coagulation | X | X[j] | X[j] | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Insulin and Lipids | X | X | | X | | X | | | X | | | X | | | X | X | X |
| HbA1c | X[k] | X | | X | | X | | | X | | | X | | | X | X | X |
| eGFR | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| HIV-1, HBV, HCV Serology | X | | | | | | | | | | | | | | | | |
| CCI | | | | | | | | | | | | | | | | | |
| CCI | | | | | | | | | | | | | | | | | |
| CCI | | | | | | | | | | | | | | | | | |
| CCI | | | | | | | | | | | | | | | | | |
| Pregnancy Testing[n] | X | X | | X | X | X | X | X | X | X | X | X | X | X | X | X | X |

| Assessments | Screening | Day 1 | On-Treatment Visits: Week 1 | Week 4 | Week 8 | Week 12 | Week 16 | Week 20 | Week 24 | Week 28 | Week 32 | Week 36 | Week 40 | Week 44 | Week 48 | ET | Follow-Up |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| CCI | | | | | | | | | | | | | | | | | |
| Urine Drug Screen | X | | | | | | | | | | | | | | | | |
| Urine Collection (albumin, creatinine, albumin/creatinine ratio) | | X | | | | X | | | X | | | X | | | X | X | X |
| CCI | | | | | | | | | | | | | | | | | |
| CCI | | | | | | | | | | | | | | | | | |
| CCI | | | | | | | | | | | | | | | | | |

a Complete PE
b Historical ultrasound within 3 months inclusive to the date of Screening may be used
CCI
e Historical liver biopsy (within 6 months of the Screening for F3 and within 12 months of the Screening for F4) may be accepted as the Screening biopsy
CCI
g To be completed upon confirmation of subject's eligibility; may be completed up to 7 days before or 3 days after Day 1

[redacted]

i AE reporting during Screening is limited to SAEs and AEs related to study procedures
j Additional testing: digoxin level at Day 1, Week 1, and as needed in subjects taking digoxin (refer to Section 5.3 of the Protocol)
k If HbA1c is unable to be resulted, serum fructosamine will be tested
[redacted]
n For female subjects of childbearing potential only. Serum pregnancy test at Screening and urine pregnancy test at Day 1 and every 4 weeks thereafter, including ET. FSH may be tested at Screening to determine a female subject's postmenopausal state (refer to Appendix 3 of the Protocol)
[redacted]

## Appendix 2. CTCAE Grade for Laboratory Parameters

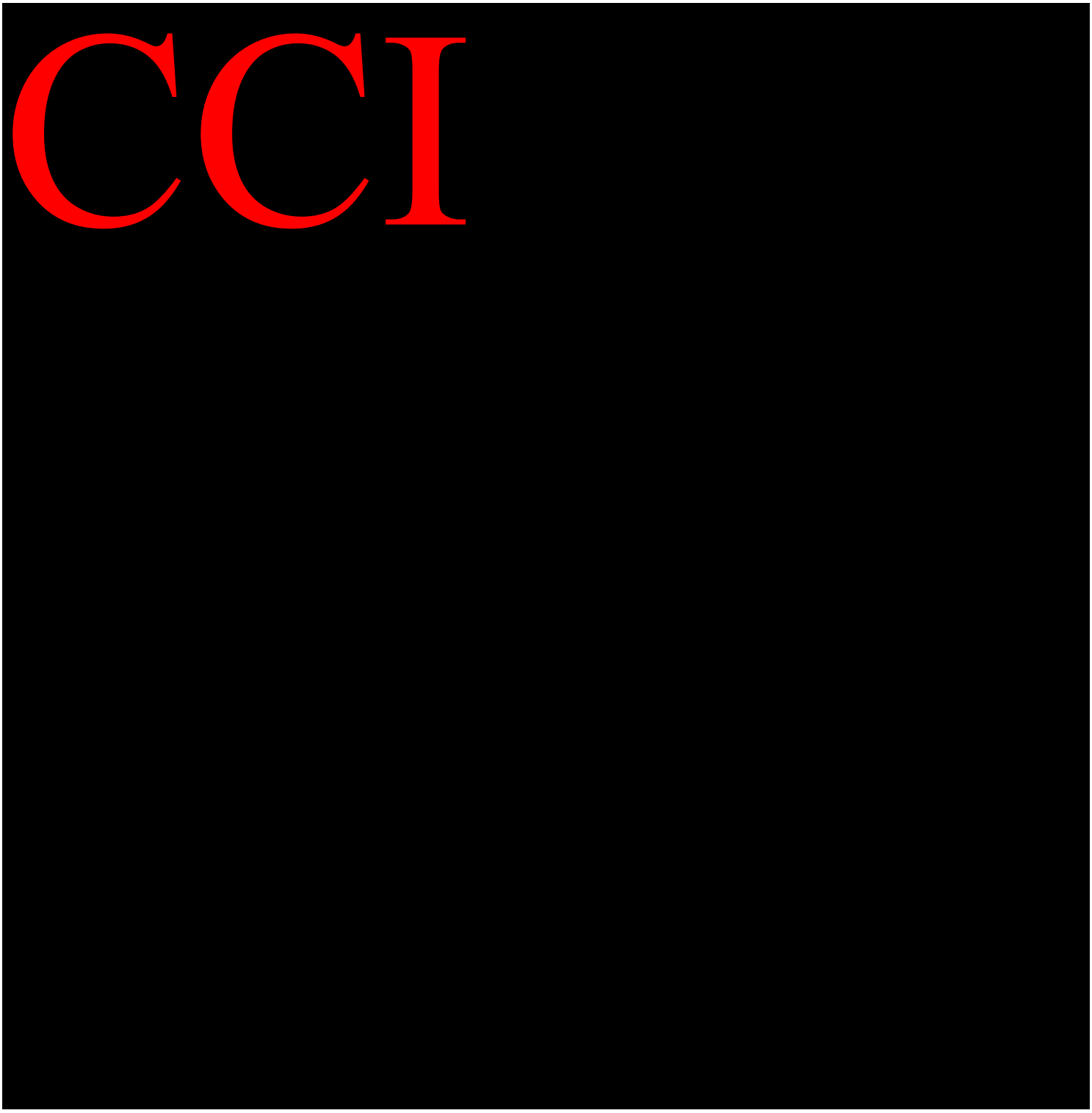
| CTCAE 5.0 | CTCAE Grade | | | | |
|---|---|---|---|---|---|
| **CTCAE Term** | **Grade 1** | **Grade 2** | **Grade 3** | **Grade 4** | **Grade 5** |
| Anemia | Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L | Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L | Hgb <8.0 g/dL;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

| CTCAE 5.0 | CTCAE Grade | | | | |
|---|---|---|---|---|---|
| **CTCAE Term** | **Grade 1** | **Grade 2** | **Grade 3** | **Grade 4** | **Grade 5** |
| CCI | | | | | |
| Haptoglobin decreased | <LLN | - | - | - | - |
| Hemoglobin increased | Increase in >0 - 2 g/dL | Increase in >2 - 4 g/dL | Increase in >4 g/dL | - | - |
| INR increased | >1.2 - 1.5; >1 - 1.5 x baseline if on anticoagulation; monitoring only indicated | >1.5 - 2.5; >1.5 - 2.5 x baseline if on anticoagulation; dose adjustment indicated | >2.5; >2.5 x baseline if on anticoagulation; bleeding | - | - |
| Lipase increased | >ULN - 1.5 x ULN | >1.5 - 2.0 x ULN; >2.0 - 5.0 x ULN and asymptomatic | >2.0 - 5.0 x ULN with signs or symptoms; >5.0 x ULN and asymptomatic | >5.0 x ULN and with signs or symptoms | - |
| Lymphocyte count decreased | <LLN - 800/mm3; <LLN - 0.8 x 10e9/L | <800 - 500/mm3; <0.8 - 0.5 x 10e9 /L | <500 - 200/mm3; <0.5 - 0.2 x 10e9 /L | <200/mm3; <0.2 x 10e9 /L | - |
| Lymphocyte count increased | - | >4000/mm3 - 20,000/mm3 | >20,000/mm3 | - | - |
| Neutrophil count decreased | <LLN - 1500/mm3; <LLN - 1.5 x 10e9 /L | <1500 - 1000/mm3; <1.5 - 1.0 x 10e9 /L | <1000 - 500/mm3; <1.0 - 0.5 x 10e9 /L | <500/mm3; <0.5 x 10e9 /L | - |
| Platelet count decreased | <LLN - 75,000/mm3; <LLN - 75.0 x 10e9 /L | <75,000 - 50,000/mm3; <75.0 - 50.0 x 10e9 /L | <50,000 - 25,000/mm3; <50.0 - 25.0 x 10e9 /L | <25,000/mm3; <25.0 x 10e9 /L | - |
| Serum amylase increased | >ULN - 1.5 x ULN | >1.5 - 2.0 x ULN; >2.0 - 5.0 x ULN and asymptomatic | >2.0 - 5.0 x ULN with signs or symptoms; >5.0 x ULN and asymptomatic | >5.0 x ULN and with signs or symptoms | - |
| White blood cell decreased | <LLN - 3000/mm3; <LLN - 3.0 x 10e9 /L | <3000 - 2000/mm3; <3.0 - 2.0 x 10e9 /L | <2000 - 1000/mm3; <2.0 - 1.0 x 10e9 /L | <1000/mm3; <1.0 x 10e9 /L | - |
| Hypercalcemia | Corrected serum calcium of >ULN - 11.5 mg/dL; >ULN - 2.9 mmol/L; Ionized 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 |

| CTCAE 5.0 | CTCAE Grade | | | | |
|---|---|---|---|---|---|
| **CTCAE Term** | **Grade 1** | **Grade 2** | **Grade 3** | **Grade 4** | **Grade 5** |
| Hyperkalemia | >ULN - 5.5 mmol/L | >5.5 - 6.0 mmol/L; intervention initiated | >6.0 - 7.0 mmol/L; hospitalization indicated | >7.0 mmol/L; life-threatening consequences | Death |
| Hypermagnesemia | >ULN - 3.0 mg/dL; >ULN - 1.23 mmol/L | - | >3.0 - 8.0 mg/dL; >1.23 - 3.30 mmol/L | >8.0 mg/dL; >3.30 mmol/L; life-threatening consequences | Death |
| Hypernatremia | >ULN - 150 mmol/L | >150 - 155 mmol/L; intervention initiated | >155 - 160 mmol/L; hospitalization indicated | >160 mmol/L; life-threatening consequences | Death |
| Hypertriglyceridemia | 150 mg/dL - 300 mg/dL; 1.71 mmol/L - 3.42 mmol/L | >300 mg/dL - 500 mg/dL; >3.42 mmol/L - 5.7 mmol/L | >500 mg/dL - 1000 mg/dL; >5.7 mmol/L - 11.4 mmol/L | >1000 mg/dL; >11.4 mmol/L; life-threatening consequences | Death |
| Hyperuricemia | >ULN without physiologic consequences | - | >ULN with physiologic consequences | Life-threatening consequences | Death |
| Hypoalbuminemia | <LLN - 3 g/dL; <LLN - 30 g/L | <3 - 2 g/dL; <30 - 20 g/L | <2 g/dL; <20 g/L | Life-threatening consequences; urgent intervention indicated | Death |
| Hypocalcemia | Corrected serum calcium of <LLN - 8.0 mg/dL; <LLN - 2.0 mmol/L; Ionized calcium <LLN - 1.0 mmol/L | Corrected serum calcium of <8.0 - 7.0 mg/dL; <2.0 - 1.75 mmol/L; Ionized calcium <1.0 - 0.9 mmol/L; symptomatic | Corrected serum calcium of <7.0 - 6.0 mg/dL; <1.75 - 1.5 mmol/L; Ionized calcium <0.9 - 0.8 mmol/L; hospitalization indicated | Corrected serum calcium of <6.0 mg/dL; <1.5 mmol/L; Ionized calcium <0.8 mmol/L; life-threatening consequences | Death |
| Hypoglycemia | <LLN - 55 mg/dL; <LLN - 3.0 mmol/L | <55 - 40 mg/dL; <3.0 - 2.2 mmol/L | <40 - 30 mg/dL; <2.2 - 1.7 mmol/L | <30 mg/dL; <1.7 mmol/L; life-threatening consequences; seizures | Death |
| Hypokalemia | <LLN - 3.0 mmol/L | Symptomatic with <LLN - 3.0 mmol/L; intervention indicated | <3.0 - 2.5 mmol/L; hospitalization indicated | <2.5 mmol/L; life-threatening consequences | Death |
| Hypomagnesemia | <LLN - 1.2 mg/dL; <LLN - 0.5 mmol/L | <1.2 - 0.9 mg/dL; <0.5 - 0.4 mmol/L | <0.9 - 0.7 mg/dL; <0.4 - 0.3 mmol/L | <0.7 mg/dL; <0.3 mmol/L; life-threatening consequences | Death |
| 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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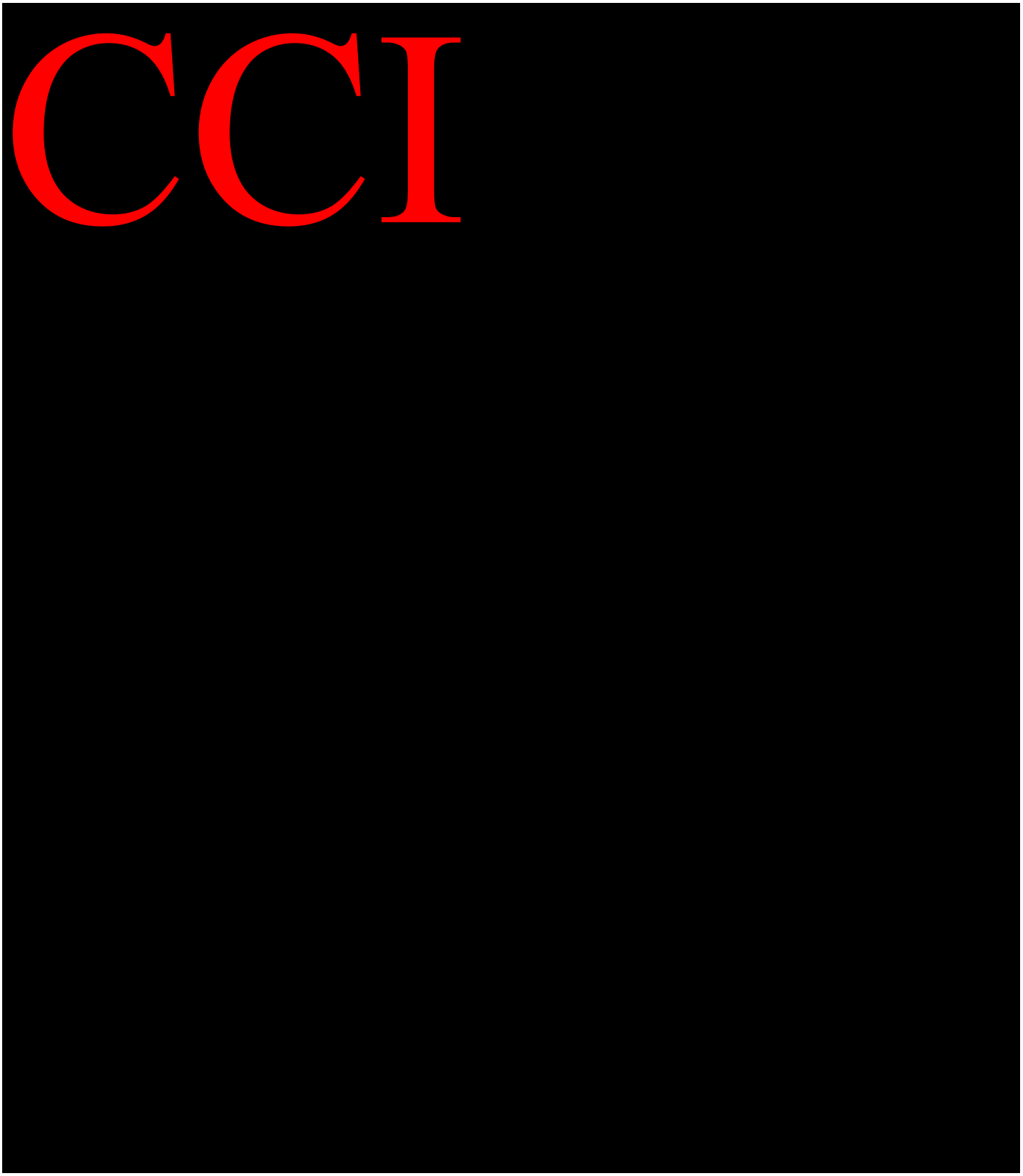
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# SAP GS-US-454-4378 v1.0

# ELECTRONIC SIGNATURES

| Signed by | Meaning of Signature | Server Date (dd-MMM-yyyy hh:mm:ss) |
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| PPD | Clinical Research eSigned | 28-May-2019 17:56:44 |