STATISTICAL ANALYSIS PLAN

Study Title:	A Proof-of-Concept, Open-Label Study Evaluating the Safety and Tolerability of Cilofexor in Subjects with Primary Sclerosing Cholangitis (PSC) and Compensated Cirrhosis
Study Phase:	1b
Name of Test Drug:	Cilofexor (CILO; GS-9674)
Study Number:	GS-US-428-5443
Protocol Version (Date):	Amendment 3 (15 January 2021)
Analysis Type:	Final Analysis
Analysis Plan Version:	Version 1.0
Analysis Plan Date:	15 December 2021
Analysis Plan Author(s):	PPD

CONFIDENTIAL AND PROPRIETARY INFORMATION

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF ABBREVIATIONS

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BLQ	below the limit of quantitation
BMI	body mass index
C4	7-alpha-hydroxy-4-cholesten-3-one
CILO	cilofexor
CLDQ	Chronic Liver Disease Questionnaire
CP	Child-Pugh
CRF	case report form
CSR	clinical study report
CTCAE	Common Toxicity Criteria for Adverse Events
DMC	data monitoring committee
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
ELF™	enhanced liver fibrosis
EQ-5D	EuroQol five dimensions
ET	early termination
FGF19	fibroblast growth factor 19
GGT	gamma glutamyl transferase
HLGT	high-level group term
HLT	high-level term
IBD	inflammatory bowel disease
ID	identification
INR	international normalized ratio
IXRS	interactive voice or web response system
LLN	lower limit of normal
LLT	lower-level term
LOQ	limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
MELD	model for end-stage liver disease
PD	pharmacodynamic
PI	principle investigator
PIIINP	procollagen III N-terminal propeptide
PK	pharmacokinetic
PRO	patient-reported outcome
PSC	primary sclerosing cholangitis
PT	preferred term

Q1, Q3	first quartile, third quartile
QoL	quality of life
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SE	standard error
SIBDQ	Short Inflammatory Bowel Disease Questionnaire
SOC	system organ class
TEAE	treatment-emergent adverse event
TFLs	tables, figures, and listings
TIMP1	tissue inhibitor of metalloproteinase 1
UC	ulcerative colitus
ULN	upper limit of normal
VAS	visual analog scale
WHO	World Health Organization

PHARMACOKINETIC ABBREVIATIONS

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

1. INTRODUCTION

This statistical analysis plan (SAP) describes the statistical analysis methods and data presentations to be used in tables, figures, and listings (TFLs) in the clinical study report (CSR) for Study GS-US-428-5443. This SAP is based on the study protocol amendment 3 dated 15 January 2021 and the electronic case report form (eCRF). The SAP will be finalized before database finalization. Any changes made after the finalization of the SAP will be documented in the CSR.

The study enrollment was terminated early by the sponsor on 30 July 2021 due to recruitment challenges in a rare disease population.

1.1. Study Objectives

The primary objective of this study is as follows:

- To assess the safety and tolerability of escalating doses of cilofexor (CILO, previously known as GS-9674) in subjects with primary sclerosing cholangitis (PSC) and compensated cirrhosis

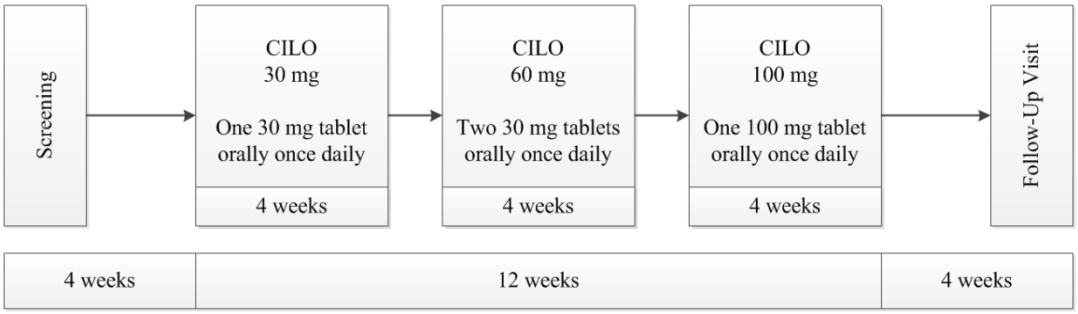
CCI [redacted]

1.2. Study Design

This is a proof of concept, open-label study evaluating the safety and tolerability of CILO in subjects with PSC and compensated cirrhosis.

Eligible subjects were enrolled and received treatment with escalating doses of CILO over 12 weeks. Subjects dose escalated at Week 4 (from 30 mg to 60 mg once daily) and Week 8 (from 60 mg to 100 mg once daily) if in the opinion of the Principal Investigator (PI) study drug had been tolerated.

The overall study design is presented graphically in the figure below.



Individual subject participation in the study can last up to 20 weeks, which includes a 4-week screening period, a 12-week treatment period (divided into three 4-week dosing stages at 30 mg QD, 60 mg QD, and 100 mg QD), and a Follow-Up visit 4 weeks after the Week 12 visit.

Study drug dosing may be interrupted for up to 4 consecutive weeks at the discretion of the PI if a subject experienced an adverse event (AE) (eg, intolerable pruritus) thought to be related to the study drug. During the period of study drug dose interruption, subjects were not required to attend in-clinic visits per the Study Procedures Table (Appendix 1) but were monitored via weekly telephone follow-up visits (refer to Section 7.5.5 of study protocol). If a study drug dose interruption required reinitiation of a dosing stage, participation in the study could be extended from up to 20 weeks to up to 28 weeks to complete 4 consecutive weeks of dosing at each dose stage.

1.3. Sample Size and Power

Due to the exploratory nature of this study, no formal power calculations were used to determine sample size.

2. TYPE OF PLANNED ANALYSIS

2.1. Interim Analyses

No interim analysis for efficacy was planned.

2.1.1. Data Monitoring Committee Analyses

This study had an internal multidisciplinary Data Monitoring Committee (DMC) to review the progress of the study and safety of the study after 10 subjects completed 4 weeks of CILO 30 mg treatment.

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

2.2. Final Analysis

The final analysis will be performed 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.

2.3. Changes from Protocol-Specified Analysis

Due to limited subject enrollment in the study, part of safety summaries and listings (body weight, vital signs, prior and concominant medications, electrocardiogram [ECG], and pharmacodynamic parameters) planned in the protocol will not be provided.

PSC Patient-Reported Outcome (PRO) is a novel endpoint. CCI [redacted]

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) or standard error (SE), median, first quartile (Q1), third quartile (Q3), minimum, and maximum will be presented.

By-subject listings will be presented for all subjects in the All Enrolled Analysis Set, and sorted by subject identification (ID) number in ascending order, visit date, and time (if applicable), unless otherwise specified. Data collected on log forms, such as AEs, will be presented in chronological order within subject. Age, sex at birth, race, and ethnicity will be included in the listings, as space permits.

3.1. Analysis Sets

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

For each analysis set, the number and percentage of subjects eligible for inclusion will be provided in the disposition table as detailed in Section 4.

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. Safety Analysis Set

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

3.1.3. Pharmacokinetic Analysis Sets

The Pharmacokinetic (PK) Analysis Sets will include all enrolled subjects who took at least 1 dose of study drug and have at least 1 nonmissing concentration value reported by the PK laboratory for the corresponding analytes. These are the primary analysis sets for all PK analyses.

CCI [redacted]

[redacted]

3.1.5. Pharmacodynamic Analysis Sets

The Pharmacodynamic (PD) Analysis Sets will include all enrolled subjects who received at least 1 dose of study drug and have at least 1 nonmissing PD value for each respective PD parameter.

CCI [redacted]

[redacted]

3.2. Strata and Covariates

This study did not use a stratified randomization schedule when enrolling subjects. No covariates will be included in efficacy and safety analyses.

3.3. Examination of Subject Subgroups

There are no prespecified subject subgroupings for analyses.

3.4. Multiple Comparisons

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

3.5. Missing Data and Outliers

3.5.1. 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. The handling of missing or incomplete dates for AE onset is described in Section 7.1.5.2.

3.5.2. Outliers

Outliers of non-PK data 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.

3.6. Data Handling Conventions and Transformations

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

- If only month and year of birth is collected, then "15" will be imputed as the day of birth.

- If only year of birth is collected, then "01 July" will be imputed as the day and month of birth.

- If year of birth is missing, then date of birth will not be imputed.

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

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

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

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

- The lower or upper 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 lower or upper LOQ).

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

Natural logarithm transformation will be used for analyzing concentrations and PK parameters in intensive PK samples, if applicable. 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 postdose time points for summary purposes.

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) and summary statistics will be displayed as "BLQ."

PK parameters that are BLQ will be imputed as one-half LOQ before log transformation or statistical model fitting, if applicable.

3.7. Analysis Visit Windows

3.7.1. 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.

Additional calculations for subjects who require a PI-approved study drug interruption are as follows. Post-interruption study day will be calculated from the first dosing date of study drug subsequent to post-interruption and derived as follows:

- For post-interruption dosing resumed from 30 mg: Assessment Date – First Post-interruption Dosing Date + 1
- For post-interruption dosing resumed from 60 mg: Assessment Date – First Post-interruption Dosing Date + 29
- For post-interruption dosing resumed from 100 mg: Assessment Date – First Post-interruption Dosing Date + 57

Therefore, the day of first post-interruption dose of study drug administration can be Post-interruption study Day 1, 29, or 57, depending on the dose level when PI-approved study drug dose interruption occurs.

3.7.2. 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.

On-treatment visit windows will be calculated from study Day 1 or the first post-interruption study drug dosing date for selected efficacy measures, elastography, and safety laboratory data.

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 early termination (ET) or Follow-Up.

The analysis windows for selected measures are provided in Table 3-1 to Table 3-3. The algorithm for assigning baseline analysis window does not apply to the liver tests (ALP, total bilirubin, ALT, AST, and GGT). For these 5 parameters, the baseline values will be determined by averaging the values obtained at Screening and Baseline/Day 1, and no specific study day is associated with the average values.

Table 3-1. Analysis Visit Windows for Chemistry, eGFR, Hematology, Coagulation, Child-Pugh (CP)/ Model for End-stage Liver Disease (MELD) Scores, Pruritus VAS, 5D-Itch and Biomarkers, Including hsCRP, ELF™ Score and Components, FibroSURE/FibroTest® and Selected Components, Bile Acids, FGF19, C4.

Nominal Visit	Nominal Study Day/Post-interruption Study Day	Visit Window Study Day/Post-interruption Study Day	
		Lower Limit	Upper Limit
Baseline/Post-interruption Day 1	1	(none)	1
Week 1/Post-interruption Week 1	8	2	18
Week 4/Post-interruption Week 4	29	19	42
Week 8/Post-interruption Week 8	57	43	70
Week 12/Post-interruption Week 12	85	71	≥85

Table 3-2. Analysis Visit Windows for IBD Symptoms

Nominal Visit	Nominal Study Day/Post-interruption Study Day	Visit Window Study Day/Post-interruption Study Day	
		Lower Limit	Upper Limit
Baseline/Post-interruption Day 1	1	(none)	1
Week 4/Post-interruption Week 4	29	2	42
Week 8/Post-interruption Week 8	57	43	70
Week 12/Post-interruption Week 12	85	71	≥85

Table 3-3. Analysis Visit Windows for QoL Questionnaires and FibroScan

Nominal Visit	Nominal Study Day/Post-interruption Study Day	Visit Window Study Day/Post-interruption Study Day	
		Lower Limit	Upper Limit
Baseline/Post-interruption Day 1	1	(none)	1
Week 12/Post-interruption Week 12	85	2	≥85

Data relating to unscheduled 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.
- For subjects who prematurely discontinue from the study, early termination (ET) data will be summarized as a separate visit, labeled as "Early Termination Visit."
- Data collected on a follow-up visit will be summarized as a separate visit and labeled "Follow-up Visit."
- Data obtained after the follow-up visit or last dose date plus 30 days (whichever is later) will be excluded from the summaries but will be included in the listings.

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

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

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

- For baseline, the last nonmissing value on or prior to the first dosing date of study drug 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 for categorical data.

- For each liver test (ALP, total bilirubin, ALT, AST, and GGT), the baseline value will be determined by averaging all values obtained between Screening and Baseline/Day 1 (inclusive). The corresponding baseline reference range will be defined as the one associated with the latest visit that was included for computing the baseline value, for the purpose of determination of the abnormality and/or toxicity grades.

- For postbaseline values:

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

  — If there are 2 or more 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 worst severity will be taken for categorical data, unless otherwise specified.

  — FGF19 and C4 obtained on the same day will not be averaged. The predose value would be selected to represent the study visit, when the data are summarized by study visit and not by timepoint within a visit. The summary by timepoint is described separately in Section 9.3.

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

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

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

4. SUBJECT DISPOSITION

4.1. Subject Enrollment and Disposition

Key study dates (ie, first subject screened, first subject enrolled, last subject enrolled, last subject last visit for the primary endpoint, and last subject last visit for the clinical study report) will be provided.

A summary of subject disposition will be provided. This summary will present the number of subjects screened, the number of subjects enrolled, and the number and percentage of subjects in each of the categories listed below. For the Safety Analysis Set category, the denominator for the percentage calculation will be the total number of subjects enrolled for each column. For all other categories, the denominator for the percentage calculation will be the total number of subjects in the Safety Analysis Set for each column.

- Safety Analysis Set
- PK Analysis Set for each analyte
- [redacted]
- PD Analysis Set for each parameter
- [redacted]
- Had PI approved study drug interruption and study drug dose level when the interruption occured
- Completed study drug
- Did not complete study drug with reasons for premature discontinuation of study drug
- Completed study
- Did not complete the study with reasons for premature discontinuation of study

In addition, the total number of subjects who were enrolled, and the number of subjects in each of the disposition categories listed above will be displayed in a flowchart.

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

- Reasons for premature study drug or study discontinuation

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.

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 (minus study drug interruption duration if there is a PI-approved study drug interruption, where the study drug interruption duration is defined as first post-interruption dosing date minus last dosing date prior to drug interruption minus 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 for subjects included in the final analyses.

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, 1 week, 4 weeks, and every 4 weeks thereafter. Summaries will be provided for the Safety Analysis Set.

4.2.2. Adherence to Study Drug

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

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

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

4.2.2.1. Prescribed Adherence

The level of prescribed adherence to the study drug regimen will be determined by the total amount of study drug administered relative to the total amount of study drug specified by the protocol for a subject who completes treatment in the study, ie, 112 tabelets. For subjects who require a study drug interruption, the adherence calculation will account for the initial drug amount and the subsequent drug amount (after the interruption) at the respective dose level. For example, if a subject takes ten 100 mg tablets and requires an interruption, and subsequently takes twelve 100 mg tablets post interruption before discontinuing, the denominator would be 122 (28 + 28 * 2 + 10 + 28, the last term 28 is because the protocol specifies that subjects should complete 28 consecutive days at each dose level).

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

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

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

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

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

4.4. Assessment of COVID-19 Impact

This study was ongoing during the novel coronavirus (COVID-19) pandemic which has an impact on the study conduct. Some subjects were unable to attend onsite visits due to shelter in place guidelines, site closures, or other reasons. This section describes how special situations due to COVID-19 will be handled in the analysis.

4.4.1. Protocol Deviations Due to COVID-19

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

5. BASELINE CHARACTERISTICS

5.1. Demographics and Baseline Characteristics

Subject demographic variables (ie, age, sex, race, and ethnicity) and baseline characteristics (body weight [in kg], height [in cm], body mass index [BMI; in kg/m^2]) will be summarized using descriptive statistics for continuous variables and using number and percentage of subjects for categorical variables. The summary of demographic data will be provided for the Safety Analysis Set.

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

5.2. Other Baseline Characteristics

Other baseline characteristics include:

- UDCA use (yes or no, based on concomitant medication page)
- ALP, GGT, ALT, AST
- Total bilirubin, direct bilirubin, albumin, INR
- Fasting bile acids
- MELD score, Child-Pugh (CP) score
- ELF™ score and components
- FibroSURE/FibroTest® and selected components
- Liver Stiffness Assessed by FibroScan
- Platelets
- Inflammatory bowel disease (IBD) history (yes or no, based on medical history data)
- Ulcerative colitus (UC) history (yes or no, based on medical history data)
- Crohn's disease history (yes or no, based on medical history data)

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

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

5.3. Medical History

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

[redacted]

CCI [redacted]

[redacted]

7. SAFETY ANALYSES

7.1. Adverse Events and Deaths

7.1.1. Adverse Event Dictionary

Clinical and laboratory AEs will be coded using the current version of the 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 AE dataset.

7.1.2. Adverse Event Severity

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

7.1.3. Relationship of Adverse Events to Study Drug

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

7.1.4. Serious Adverse Events

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

7.1.5. Treatment-Emergent Adverse Events

7.1.5.1. Definition of Treatment-Emergent Adverse Events

Treatment-emergent adverse events (TEAEs) 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.

A brief, high-level summary of the number and percentage of subjects who experienced at least 1 TEAE in the categories described below will be provided. All deaths observed in the study will also be included in this summary.

- TEAE
- TEAEs with Grade 2 or higher
- TEAEs with Grade 3 or higher
- TE treatment-related AEs
- TE treatment-related AEs with Grade 2 or higher
- TE treatment-related AEs with Grade 3 or higher
- TE SAEs
- TE treatment-related SAEs
- TEAEs leading to premature discontinuation of study drug
- TEAEs leading to temporary interruption of study drug
- Death

The number and percentage of subjects who experienced at least 1 TEAE will be provided and summarized by SOC and PT for the AE categories described below:

- TEAE
- TEAEs with Grade 2 or higher
- TE treatment-related AEs
- TE SAEs
- TEAEs leading to premature discontinuation of study drug
- TEAEs leading to temporary interruption of study drug

Summaries of all TEAEs by PT only, and by SOC, PT, and maximum severity will also be provided.

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 (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, data listings will be provided for the following:

- All AEs, indicating whether the event is treatment emergent
- All TEAEs with severity of Grade 2 or higher
- All SAEs
- All deaths
- All AEs leading to premature discontinuation of study drug
- All AEs leading to temporary interruption of study drug

7.2. Laboratory Evaluations

Laboratory data collected during the study will be analyzed and summarized using both quantitative and qualitative methods. Summaries of laboratory data will be provided for the Safety Analysis Set and will include data collected up to the last dose of study drug plus 30 days. The analysis will be based on values reported in conventional units. When values are BLQ, 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 3.6. 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, eGFR, serum chemistry, coagulation, and urinalysis separately. Values falling outside of the relevant reference range and/or having a severity grade of 1 or higher on the Common Toxicity Criteria for Adverse Events (CTCAE) severity grade as described in Appendix 2 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 for laboratory tests will not be provided.

7.2.2. Graded Laboratory Values

The CTCAE Version 5.0 will be used to assign toxicity grades (0 to 4) to laboratory results for analysis. Grade 0 includes all values that do not meet the criteria for an abnormality of at least Grade 1. For laboratory tests with criteria for both increased and decreased levels, analyses for each direction (ie, increased, decreased) will be presented separately.

For the baseline ALP, total bilirubin, GGT, ALT and AST toxicity grades, the CTCAE version 5.0 will be used to assign 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. 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. 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; subjects will be categorized according to the most severe postbaseline abnormality grade for a given lab test:

- Graded 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 or abnormal flags displayed.

7.2.3. Liver-related Laboratory Evaluations

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

For subjects with normal baseline ALT/AST (≤ ULN):

- Subjects meeting criteria for close observation
  - ALT/AST > 3 × ULN
- Subjects meeting any one of the following criteria for withholding study drug
  - ALT/AST > 8 × ULN
  - ALT/AST > 5 × ULN for 2 weeks
  - ALT/AST > 3 × ULN and total bilirubin > 2 × ULN (or 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 elevated baseline ALT/AST (> ULN)

- Subjects meeting criteria for close observation
  - ALT/AST > 2 × Baseline or > 300 U/L
- Subjects meeting any one of the following criteria for withholding study drug
  - ALT/AST > 8 × Baseline or > 500 U/L
  - ALT/AST > 3 × Baseline or > 300 U/L, and total bilirubin > 2 × ULN (or direct bilirubin > 2 x Baseline in subjects with Gilbert's syndrome)
  - ALT/AST > 3 × Baseline or > 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 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. Body Weight and Vital Signs

Body weight and vital signs will not be summarized or listed.

7.4. Prior and Concomitant Medications

Prior and concomitant medications will not be summarized or listed.

7.5. Electrocardiogram Results

Electrocardiogram data will not be summarized or listed.

7.6. Other Safety Measures

A by-subject listing sorted by subject ID number will be provided for subjects who become pregnant during the study.

IBD Symptom Severity Assessment is a survey for the assessment of IBD that considers stool frequency, rectal bleeding, and physician assessment of IBD for disease severity assessment. A by-subject listing of IBD Symptom Severity Assessment will be provided by subject ID number and visit in chronological order for subjects with history of IBD.

[redacted]


CCI

[redacted]

10. 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.

11. SOFTWARE

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

Phoenix WinNonlin® 8.2. Pharsight Corporation, Princeton, NJ, USA.

12. SAP REVISION

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

13. APPENDIX

Appendix 1. Study Procedures Table

Study Procedures Table – Screening to Follow-Up Visit

Assessments	Screening[a]	Treatment Visits (± 3 days)[b c d]						Follow-Up (± 5 days)
		Baseline/ Day 1	Week 1	Week 4	Week 8	Week 12	ET[e]	
Subject Fasting		X	X	X	X	X	X	X
Written Informed Consent	X							
Medical History	X							
Review Inclusion/Exclusion Criteria	X	X						
Physical Examination[f]	X	X	X	X	X	X	X	X
Assess ascites and HE	X	X	X	X	X	X	X	X
CP and MELD Scores	X	X	X	X	X	X	X	X
Vital Signs[g] and Body Weight	X	X	X	X	X	X	X	X
Height	X							
IBD Symptom Severity Assessment[h]	X	X		X	X	X	X	X
CCI								
Review for Active IBD[j]		X	X	X	X	X	X	X
12-lead ECG	X	X						
CCI								
Concomitant Medications	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X
Dispense Study Drug		X		X	X			

Assessments	Screening[a]	Treatment Visits (± 3 days)[b c d]						Follow-Up (± 5 days)
		Baseline/ Day 1	Week 1	Week 4	Week 8	Week 12	ET[e]	
Review Study Drug Compliance			X	X	X	X	X	
Laboratory Assessments								
Chemistry, eGFR, Hematology, Coagulation Panel	X	X	X	X	X	X	X	X
Lipid Profile		X		X	X	X	X	X
C-Peptide, Insulin and HbA_{1c}		X				X	X	X
HIV-1, HBV and HCV Serology	X							
Urine Drug Screen	X							
Pregnancy Testing[l]	X	X		X	X	X	X	X
Serum FSH[m]	X							
Stool Collection (if available)		X				X		
Blood for Biomarkers	X	X	X	X	X	X	X	X
CCI								
CCI								

AE = adverse event; CLDQ = Chronic Liver Disease Questionnaire; CP = Child-Pugh; ECG = electrocardiogram; EDC = electronic data capture; eGFR = estimated glomerular filtration rate; EQ-5D = EuroQol five dimensions; ET = early termination; FSH = follicle-stimulating hormone; HBV = hepatitis B virus; HbA_{1c} = hemoglobin A_{1c}; HCV = hepatitis C virus; HE = hepatic encephalopathy; HIV-1 = human immunodeficiency virus type 1; IBD = inflammatory bowel disease; IWRS = interactive web response system; MELD = model for end-stage liver disease; PD = pharmacodynamic(s); PE = physical examination; PI = principal investigator; PK = pharmacokinetic(s);

PRO = patient-reported outcome; PSC = primary sclerosing cholangitis; QoL = quality of life; SIBDQ = short inflammatory bowel disease questionnaire; VAS = visual analog scale

a Subjects will be screened up to 4 weeks prior to treatment. The screening period may be extended under special circumstances with the explicit approval of the medical monitor.

b At the discretion of the PI, study drug dosing may be temporarily interrupted if subject experiences an AE thought to be related to study drug, including pruritus. In the event this occurs, the PI should notify the medical monitor and the subject should hold study drug until the AE has resolved or pruritus has returned to baseline levels. When resuming study drug, the subject should resume dosing at the prior dose and restart a 4-week challenge on this dose. If subject tolerates study drug for the subsequent 4 weeks, the subject may dose escalate at the discretion of the PI (refer to Section 7.5.5 of the protocol). The same in-clinic visits and associated study assessments during regular visits would be performed when re-challenging a dose (referenced as postinterruption visit in IWRS and EDC). If reinitiating dose stage of 30 mg study drug, subjects are not required to redo Baseline/Day1 QoLs.

c Telephone follow-up visit will occur only for subjects on PI approved study drug dose interruption. During the period of study drug dose interruption, subjects will be contacted on a weekly basis for up to 4 consecutive weeks (refer to Section 6.4.2 of the protocol).

d Treatment visits windows are ±3 days unless otherwise stated (see Section 6.4 of the protocol).

e Subjects prematurely discontinuing from the study should complete an ET visit within 30 days of last study visit.

f Symptom-directed PE. The focus of a symptom-driven physical examination will be determined by the investigator based on subject complaint. A complete PE will be completed at screening.

g Vital signs include heart rate, systolic and diastolic blood pressure, respiratory rate, and body temperature.

h For subjects with history of IBD. Assessment of Bleeding History and Daily Bowel Movement Count as detailed in Appendix 6 of the protocol.

[redacted]

i For subjects with history of IBD, any evidence of active IBD seen on routinely performed colonoscopy will be captured.

[redacted]

l Females of childbearing potential only (see Appendix 4 of the protocol). Serum pregnancy tests at screening and urine pregnancy tests at Day 1, Weeks 4, 8, 12 while on treatment. Urine pregnancy test to be taken at home every 2 weeks during PI approved study drug dose interruption.

m Women of any age with amenorrhea of ≥ 12 months (see Appendix 4 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	-	-
Alanine aminotransferase increased	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	-
Alkaline phosphatase increased	>ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal	>2.5 - 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	-
Aspartate aminotransferase increased	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	-
Blood bicarbonate decreased	<LLN and no intervention initiated	-	-	-	-
Blood bilirubin increased	>ULN - 1.5 x ULN if baseline was normal; > 1.0 - 1.5 x baseline if baseline was abnormal	>1.5 - 3.0 x ULN if baseline was normal; >1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 10.0 x ULN if baseline was normal; >3.0 - 10.0 x baseline if baseline was abnormal	>10.0 x ULN if baseline was normal; >10.0 x baseline if baseline was abnormal	-
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**
GGT increased	>ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal	>2.5 - 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	-
Haptoglobin decreased	<LLN	-	-	-	-
Hemoglobin increased	Increase in >0 - 2 g/dL	Increase in >2 - 4 g/dL	Increase in >4 g/dL	-	-
INR increased	>1.2 - 1.5; >1 - 1.5 x baseline if on anticoagulation; monitoring only indicated	>1.5 - 2.5; >1.5 - 2.5 x baseline if on anticoagulation; dose adjustment indicated	>2.5; >2.5 x baseline if on anticoagulation; bleeding	-	-
Lipase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN; >2.0 - 5.0 x ULN and asymptomatic	>2.0 - 5.0 x ULN with signs or symptoms; >5.0 x ULN and asymptomatic	>5.0 x ULN and with signs or symptoms	-
Lymphocyte count decreased	<LLN - 800/mm3; <LLN - 0.8 x 10e9/L	<800 - 500/mm3; <0.8 - 0.5 x 10e9 /L	<500 - 200/mm3; <0.5 - 0.2 x 10e9 /L	<200/mm3; <0.2 x 10e9 /L	-
Lymphocyte count increased	-	>4000/mm3 - 20,000/mm3	>20,000/mm3	-	-
Neutrophil count decreased	<LLN - 1500/mm3; <LLN - 1.5 x 10e9 /L	<1500 - 1000/mm3; <1.5 - 1.0 x 10e9 /L	<1000 - 500/mm3; <1.0 - 0.5 x 10e9 /L	<500/mm3; <0.5 x 10e9 /L	-
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.
Note: Refer to Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0, which can be found at https://evs nci.nih.gov/ftp1/CTCAE/CTCAE_5.0

Appendix 3. Programming Specifications

CCI

[redacted]

CCI

[redacted]

CCI [redacted]

CCI [redacted]

[redacted]

SAP GS-US-428-5443 v.1.0

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Clinical Research eSigned	15-Dec-2021 00:02:32
PPD	General Other	15-Dec-2021 03:01:18
PPD	Clinical Pharmacology eSigned	18-Dec-2021 20:12:34
PPD	Biostatistics eSigned	20-Dec-2021 08:21:58