STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 2, Double-Blind, Randomized Study Evaluating the Safety, Tolerability, and Efficacy of GS-4997 in Combination with Prednisolone versus Prednisolone Alone in Subjects with Severe Alcoholic Hepatitis (AH)
Name of Test Drug:	Selonsertib (ASK1 Inhibitor, formerly GS-4997)
Study Number:	GS-US-416-2124
Protocol Version (Date):	Original: 12 April 2016 Amendment 1: 02 June 2016 Amendment 2: 11 January 2017 Amendment 3: 04 August 2017
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LIST OF ABBREVIATIONS

AE	adverse event
AH	alcoholic hepatitis
ALT	alanine aminotransferase
ASK1	Apoptosis Signal-regulating Kinase 1
AST	aspartate aminotransferase
AUDIT	Alcohol Use Disorders Identification Test
BAP	Biomarker Analysis Plan
bpm	beats per minute
BLQ	below the limit of quantitation
BMI	body mass index
CFR	Code of Federal Regulations
CI	confidence interval
CK-18	cytokeratin-18 fragment level
CPT	Child-Pugh-Turcotte
CSR	clinical study report
CTCAE	Common Toxicity Criteria for Adverse Events
DF	discriminant function
DMC	Data Monitoring Committee
eCRF	electronic case report form
ECG	Electrocardiogram
ELF™	enhanced liver fibrosis test
ET	early termination
FAS	full analysis set
GGT	gamma-glutamyl transferase
HbA1c	glycated hemoglobin
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HDL	high-density lipoprotein
Hgb	Hemoglobin
HIV	human immunodeficiency virus
HLGT	high-level group term
HLT	high-level term
HRS	hepatorenal syndrome
ICH	International Conference on Harmonization (of Technical Requirements for Registration of Pharmaceuticals for Human Use)
INR	international normalized ratio
IWRS	interactive web response system
LDL	low-density lipoprotein
LLT	lower-level term

LOCF	last observation carried forward
LOQ	limit of quantitation
LOXL2	serum lysyl-oxidase-like 2
LPS	Lipopolysaccharides
MedDRA	Medical Dictionary for Regulatory Activities
MELD	Model for End-Stage Liver Disease
mITT	modified Intent-to-Treat
mmHg	millimeters of mercury
PK	Pharmacokinetics
PKEX	pharmacokinetics study drug administration page
PLA	Placebo (to match selonsertib)
PRED	Prednisolone
PT	preferred term
Q1, Q3	first quartile, third quartile
QD	once daily
SADQ	Severity of Alcohol Dependence Questionnaire
SAP	statistical analysis plan
SBP	spontaneous bacterial peritonitis
SAE	serious adverse event
SD	standard deviation
SEL	Selonsertib (formerly GS-4997)
SOC	system organ class
SOW	statement of work
TEAE	treatment-emergent adverse event
TFLs	tables, figures, and listings
ULN	upper limit of normal
VLDL	very low-density lipoprotein
WBC	white blood cells
WHO	World Health Organization

PHARMACOKINETIC ABBREVIATIONS

AUC_{tau}	area under the concentration versus time curve over the dosing interval
C_{last}	last observed quantifiable concentration of the drug in plasma
C_{max}	maximum observed concentration of the drug in plasma
C_{tau}	observed drug concentration at the end of the dosing interval
T_{last}	time (observed time point) of C_{last}
T_{max}	time (observed time point) of C_{max}
λ_z	terminal elimination rate constant, estimated by linear regression of the terminal elimination phase of the plasma concentration of drug versus time curve
$t_{1/2}$	estimate of the terminal elimination half-life of the drug in plasma, calculated by dividing the natural log of 2 by the terminal elimination rate constant (λ_z)
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 (for selonsertib only)

1. INTRODUCTION

This statistical analysis plan (SAP) describes the statistical analysis methods and data presentations to be used in tables, figures, and listings (TFLs) for the final analysis for Study GS-US-416-2124 which will be conducted after all subjects complete their Week 24 study visit and/or Week 24 subject status form or prematurely discontinue from study. This SAP is based on Amendment 3 of the study protocol dated 04 August 2017 and the electronic case report form (eCRF). The SAP will be finalized before the database is finalized. Any changes made after the finalization of the SAP will be documented in the clinical study report (CSR).

1.1. Study Objectives

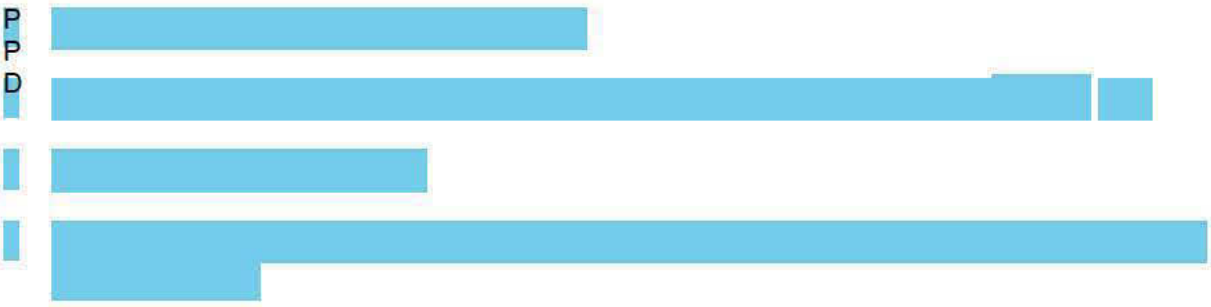
The primary objective of the study is:

- To evaluate the safety and tolerability of selonsertib in combination with prednisolone versus prednisolone alone in subjects with severe alcoholic hepatitis (AH)

The secondary objectives of the study are:

- To assess changes in hepatic synthetic function (liver biochemistry, Model for End-Stage Liver Disease [MELD] score, Child-Pugh-Turcotte [CPT] score, the Lille model, and Maddrey's Discriminant Function [DF]);
- To assess mortality at 28 days and at 8, 12, and 24 weeks;
- To determine the incidence of liver transplantation;
- To determine the incidence of hepatorenal syndrome (HRS);
- To determine the incidence of infection;
- To assess length of initial hospital stay.

The exploratory objectives of the study are as follows:



1.2. Study Design

This is a Phase 2, randomized, double-blind, proof-of-concept study evaluating the safety, tolerability, and biological activity of selonsertib in combination with prednisolone versus prednisolone alone in subjects with severe, histologically-confirmed AH. Subjects are 18 to 70 years of age, with a history of excessive alcohol consumption (average of > 40 g/day of alcohol for women and > 50 g/day of alcohol for men); AST ≥ 50 and ≤ 400 U/L; ALT ≤ 300 U/L; AST/ALT ratio ≥ 1.5; onset of jaundice within the past 3 months; a screening Maddrey DF score ≥ 32 and ≤ 60; and a MELD score ≤ 30. Subjects consented under Amendment 1 of the study protocol will qualify for the study and be stratified based on the screening MELD score calculated using central laboratory results while all other subjects will qualify for the study and be stratified based on the screening MELD score calculated using local laboratory results. All analyses of laboratory values for efficacy and safety will be based on central laboratory (ie, Covance Laboratories, Inc.) results except for the specific cases for Lille and MELD scores described in Section 3.6.1.

Up to 120 subjects will be randomized to obtain 100 subjects with histologically-proven severe AH who are evaluable for the Full Analysis Set (FAS). Subjects meeting the study's entry criteria will be randomly assigned within strata (screening MELD < 25 or ≥ 25) to one of the following 2 treatment groups in a 1:1 ratio:

- Group A (n = 50-60): Selonsertib 18 mg QD + Prednisolone 40 mg QD for 28 days
- Group B (n = 50-60): Selonsertib Placebo QD + Prednisolone 40 mg QD for 28 days

The screening and randomization phase will take approximately 2 weeks; and study drugs will be administered for a total of 28 days. Subjects will be followed for a total of 24 weeks (ie, 20 weeks following last dose of study drug); with the exception of subjects who have a biopsy that is consistent with an alternative etiology for liver disease; and those with positive serologies for HBsAg, HIV, or hepatitis C virus (HCV)—these subjects will be followed to last dose date plus 30 days for safety evaluation. Laboratory results (serum chemistry, hematology, coagulation tests), calculation of MELD, CPT (includes clinical assessments of hepatic encephalopathy and ascites) and Maddrey DF scores, and collection of vital signs, alcohol consumption, and concomitant medications and assessment of HRS and infections will be performed at screening, Day 1, Weeks 1, 2, 3, 4, 6 and 8 and every 4 weeks thereafter through Week 24. Lille score will be calculated at Weeks 1, 2, 3, and 4. Adverse events will be collected through the last dose date of any study drug plus 30 days. Serious adverse events (SAEs) not related to study endpoints will be collected up to last dose date + 30 days. Adverse events and SAEs related to study endpoints (eg, deaths, infections, and HRS) will be collected throughout the study. Insulin, lipid profiles, and weight will be collected at screening, baseline, and at Weeks 4, 12, and 24. HbA1c will follow the lipid schedule, but will not be collected at screening or Week 4. Investigator assessment of 12-lead electrocardiograms (ECG) will be collected at screening, baseline and at Weeks 4 and 8. Pregnancy testing for women of childbearing potential will be performed at screening (serum), Day 1, and every 4 weeks throughout the study.

ELF score will be collected at baseline, and at Weeks 4, 12 and 24; and the Alcohol Use Disorders Identification Test (AUDIT) and Severity of Alcohol Dependence Questionnaire (SADQ) will be administered at screening to determine levels of alcohol use and dependence on alcohol.

Single PK samples will be collected on Day 1 and at Weeks 1, 2, and 4. Subjects participating in the PK substudy will have a full profile collected between Weeks 1 and 3 of the study.

1.3. Sample Size and Power

The number of subjects was chosen based on clinical experience with other similar proof of concept studies. PPD

2. TYPE OF PLANNED ANALYSIS

2.1. Data Monitoring Committee Analyses

An independent external Data Monitoring Committee (DMC) that included 2 hepatologists and a PhD statistician convened prior to study start, once 20 subjects had completed Study Day 28, and every 3 months thereafter to review the progress of the study and perform interim reviews of safety data in order to protect subject welfare and preserve study integrity.

The DMC additionally evaluated trial stopping criteria, based on an unblinded review of safety data, and recommend early termination of the trial if there was a > 20% higher percentage of subjects in the SEL + PRED group than in the PLA + PRED group with: 1) Grade 3 or higher treatment-emergent, treatment-related adverse event(s) of a specified type, excluding evaluation of liver function, that led to premature discontinuation of selonsertib/placebo; 2) Death on/prior to Study Day 28; 3) Lille score > 0.85 while on study drug; or 4) post-baseline selonsertib/placebo laboratory stopping criteria (ie, ALT or AST > 500 U/L, ALT or AST > 5 x baseline [confirmed on repeat testing], and/or total bilirubin > 3 x baseline or nadir [confirmed on repeat testing]). See Section 7.1.7 of this SAP.

The DMC was to recommend to the sponsor whether the nature, frequency, and severity of adverse effects associated with study treatment warranted the early termination of the study in the best interests of the participants, whether the study should continue as planned, or whether the study should continue with modifications.

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

2.2. Internal Administrative Interim Analysis

An administrative interim analysis of efficacy and safety data was performed by the external statistician and reviewed by 2 individuals from Gilead. The purpose of this analysis was to assess the efficacy and safety of selonsertib + prednisolone in alcoholic hepatitis to support further planning and development of selonsertib for this indication. The 2 unblinded individuals from Gilead were independent of the GS-US-416-2124 study team and were not directly involved in routine study conduct. Individuals from Gilead who were unblinded were documented on an unblinding form, and the rationale for performing the internal interim analysis was documented per Gilead standard operating procedures. The Study Team remained blinded to treatment assignment until after the primary analysis (ie, all subjects had completed through the later of their Week 8 study visit, last dose date plus 30 days, or prematurely terminated from study) database had been finalized and the study was unblinded for the primary analysis.

2.3. Primary Analysis

The primary analysis was conducted once all subjects completed the later of their safety follow-up visit 30 days following their last dose of study drug or Week 8 study visit; or they prematurely terminated from study. All data collected with onset/visit dates on/prior to 16 February 2018 (the date the last subject completed their Week 8 visit) were included in the database snapshot for the primary analysis. All outstanding data queries were resolved or adjudicated as unresolvable, and the data was cleaned and finalized. Treatment assignments were unblinded and TFLs were displayed by treatment group.

2.4. Final Analysis

After all subjects complete the study, outstanding data queries will be resolved or adjudicated as unresolvable, 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 (PPD) 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 Safety Analysis Set unless otherwise specified. Listings will be 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 the primary analysis. The analysis set will be identified and included as a subtitle of each table, figure, and listing.

The number of subjects eligible for each analysis set will be provided by treatment group. Subjects who were excluded from the safety/mITT or FAS analysis sets will be summarized or provided in a by-subject listing.

3.1.1. All Randomized Analysis Set

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

3.1.2. Modified Intent to Treat Analysis Set

The modified Intent to Treat (mITT) analysis set includes all subjects who were randomized and took at least 1 dose of study drug. The mITT analysis set is the same as the safety analysis set provided that all subjects receive their assigned treatment. This will be the secondary analysis set for efficacy analyses.

3.1.3. Full Analysis Set

The Full Analysis Set (FAS) includes all subjects who took at least 1 dose of study drug, and had histologically-confirmed severe AH. This is the primary analysis set for efficacy analyses.

3.1.4. Safety Analysis Set

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

3.1.5. Pharmacokinetic Analysis Set

The Pharmacokinetic (PK) Analysis Set will include all randomized subjects who took at least 1 dose of selonsertib and have at least 1 nonmissing postdose concentration value reported by the PK laboratory for selonsertib or the primary metabolite GS-607509.

3.1.6. Pharmacokinetic Substudy Analysis Set

The PK Substudy Analysis Set will include all randomized subjects who took at least 1 dose of selonsertib, participated in the PK substudy, and have at least 1 nonmissing steady state PK parameter for selonsertib or the primary metabolite GS-607509. This is the primary analysis set for detailed PK analysis that uses intensive PK sampling.

3.2. Subject Grouping

For analyses based on the mITT and 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 their randomized treatment except when their actual treatment differs from randomized treatment for the entire treatment duration. In this case, subjects will be grouped based on actual treatment received.

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 web response system (IWRS) in a 1:1 ratio using a stratified randomization schedule. Stratification will be based on the screening MELD score as follows:

- Screening MELD score < 25
- Screening MELD score ≥ 25

Subjects enrolled under Amendment 1 of the protocol (eg, Subject IDs PPD PPD and PPD will utilize Covance laboratory results for calculation of screening MELD score; all other subjects will utilize local laboratory results for calculation of screening MELD score for the purposes of assignment to randomization stratum.

Death by Day 28 and by Week 8 will be summarized by randomization stratum as described in Section 3.4. If there are discrepancies in stratum assignment between the IWRS and the calculated value, the stratum assigned based on the database-calculated screening MELD score (as described above) will be used for analysis.

3.4. Examination of Subject Subgroups

Death by Day 28 and by Week 8; and Lille score broken into 3 categories (< 0.16 [complete responder]; 0.16 to < 0.56 [partial responder]; and ≥ 0.56 [null responder]) at Week 1, Week 2, and Week 4 (LOCF) will be explored for the FAS by treatment group for the following baseline characteristics:

- age (< 50 or ≥ 50 years)
- sex (male, female)
- race (White, Asian, other)
- baseline total bilirubin (< 14 mg/dL, ≥ 14 mg/dL)
- baseline prothrombin time (< 16.3 secs, ≥ 16.3 secs)
- baseline Maddrey's DF (< 38, ≥ 38)
- baseline albumin (< 3.0 mg/dL, ≥ 3.0 mg/dL)
- baseline creatinine (< 0.75 mg/dL, ≥ 0.75 mg/dL)
- baseline CPT (scores < 10 [Class A and B], ≥ 10 [Class C])
- baseline infection (yes or no)
- baseline sodium (< 135 µmol/L, ≥ 135 µmol/L)
- baseline MELD (< 21 or ≥ 21)
- baseline platelets (≤ 100 $\times 10^3/\mu L$, > 100 $\times 10^3/\mu L$)
- baseline ascites (none, any)
- baseline hepatic encephalopathy (none, any)
- baseline cirrhosis (no, yes, unknown)

Cirrhosis will be determined from the liver biopsy eCRF, and will be defined as a Metavir score of F4 or an Ishak score of F5 or F6. If no fibrosis staging was performed, cirrhosis status will be unknown.

Death by Study Day 28 and by Week 8 will also be explored by the following 2 postbaseline characteristics by treatment group:

- randomization stratum (screening MELD < 25 and ≥ 25)
- Lille score broken into 3 categories (< 0.16 [complete responder]; 0.16 to < 0.56 [partial responder]; and ≥ 0.56 [null responder]) at Week 1. Subjects with missing Lille score values at Week 1 will be considered to be null responders.

3.5. Multiple Comparisons

PPD

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, except for the cases described below.

For subjects who are missing a baseline central laboratory-calculated MELD score, the subject's screening local laboratory-calculated MELD score used to assess inclusion and exclusion criteria and to stratify the subject for randomization will be used in place of the missing central laboratory-calculated baseline MELD score.

For Lille scores, if the Week 1 Lille score for an individual subject cannot be calculated using central laboratory data and a Week 1 Lille score using local laboratory data is available, then Lille scores for that subject will be calculated using local laboratory data for all Lille score timepoints (eg, at Weeks 1, 2, 3, and 4). If both central and local laboratory Week 1 Lille scores are not calculable, then central laboratory data will be used to calculate Lille scores for all visits.

Individual subjects for whom the above imputation rules will be applied will be outlined in the Programming and Analysis Specifications (Appendix 2 of this SAP), along with the reason for their imputation.

For subjects missing a last dose date of study drug, imputation rules are described in Section 4.2.1. The handling of missing or incomplete dates for AE onset is described in Section 7.1.5.2, and for missing start dates 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. All data, including outliers, will be included in analyses.

3.7. Data Handling Conventions and Transformations

In general, age (in years) on the date of the first dose of study drug will be used for analysis and presentation in listings. If a randomized subject was not dosed with any study drug, the baseline assessment date will be used for calculating age. For screen failures, date informed consent was signed will be used for calculating age. If only birth year is collected on the eCRF, "01 July" will be used for the unknown birth day and month for the purpose of age calculation, unless age is captured on the CRF. If only birth month and year are collected on the eCRF, "01" will be used for the unknown birth date for the purpose of age calculations unless age is captured on the eCRF.

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

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

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

- The LOQ will be used for calculation of descriptive statistics if the datum is reported in the form of "≤ x" or "≥ x" (where x is considered the LOQ).

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 plasma 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 lower LOQ (LLOQ) at postbaseline time points, where LLOQ is corrected for the dilution factor (ie, reported LLOQ/dilution factor) for determination of summary and order statistics.

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."

3.8. Analysis Visit Windows

3.8.1. Definition of Study Day

Study day will be calculated from the date of first dose of selonsertib/placebo (SEL/PLA) study drug as follows:

- For postdose study days: Assessment Date – First Dose Date SEL/PLA + 1
- For days prior to the first dose: Assessment Date – First Dosing Date SEL/PLA

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

In the event that SEL/PLA and prednisolone (PRED) study drug were not started on the same date, the date of first dose of SEL/PLA will be used as the date of first dose of study drug since subjects are allowed (per protocol Amendment 2) to take "pre-doses" of commercial prednisolone for up to 3 days prior to starting study drug.

The last dosing date for an individual study drug (ie, SEL/PLA or PRED) will be the end date recorded for that study drug on the study drug administration eCRF where the "subject permanently discontinued" flag is marked 'Yes'. The last dosing date for any study drug will be the maximum of the last dosing dates for SEL/PLA and PRED.

If the last dosing date of SEL/PLA or PRED is missing or incomplete, the date of last dose will be estimated using the maximum of nonmissing study drug start or stop dates (for the study drug of interest), visit dates, and laboratory collection dates (posttreatment visits and unscheduled visits are not included).

3.8.2. Analysis Visit Windows

Subject visits might not occur on protocol-specified days. Therefore, for purposes of analysis, observations will be assigned to visit windows.

In general, the baseline value will be the last nonmissing value on or prior to the first dose date of SEL/PLA study drug. When the Screening and Day 1 visits are conducted on the same date, the later time value for Covance laboratory values should be used for purposes of analysis since the date/time is prior to first dose date/time from the pharmacokinetic study drug administration (PKEX) eCRF for all 4 subjects (eg, Subject IDs PPD PPD PPD and PPD

Analysis windows for efficacy measures of hepatic synthetic function (ie, ALT, AST, GGT, alkaline phosphatase, total bilirubin, direct bilirubin, albumin, INR, MELD, CPT, and Maddrey's DF), Lille score and recidivism to alcohol are displayed in column 2 of Table 3-1.

The analysis visit windows for liver fibrosis markers (ie, ELF score and its components) are displayed in the third column of Table 3-1.

The analysis visit windows for safety laboratory tests and vital signs will include laboratory values collected up to last dose date of any study drug + 7 days for "on-treatment" visit windows. Values that are collected ≥ 8 days after the last dose date of study regimen will be assigned to follow up visits, where FU day is defined as:

FU Day = Laboratory assessment date – Last Dose Date of Any Study Drug

For analyses of laboratory parameters that are both efficacy and safety variables (eg, hepatic synthetic function tests, and HbA1c), absolute value and change from baseline visit windows will be calculated from Study Day 1; while toxicity grading summaries will utilize safety analysis visit windows.

For all safety analyses related to laboratory toxicity grading, laboratory data collected up to 30 days after the date of last dose of any study drug will be included.

Visit windows for safety laboratory tests are displayed in the fourth column of Table 3-1.

Table 3-1. Analysis Visit Windows

Analysis Visit	Visit Windows for Hepatic Synthetic Function, Lille Scores, and Recidivism to Alcohol	Visit Windows for Liver Fibrosis Markers	Visit Windows for Vital Signs and Safety Laboratory tests (Hematology, Chemistry, Coagulation, and Lipids)
Baseline	Study Day ≤ 1	Study Day ≤ 1	Study Day ≤ 1
Week 1	2 ≤ Study Day ≤ 10	N/A	2 ≤ Study Day ≤ 10
Week 2	11 ≤ Study Day ≤ 17	N/A	11 ≤ Study Day ≤ 17
Week 3	18 ≤ Study Day ≤ 24	N/A	18 ≤ Study Day ≤ 24
Week 4	25 ≤ Study Day ≤ 34	2 ≤ Study Day ≤ 55	25 ≤ Study Day ≤ 38
Week 6	35 ≤ Study Day ≤ 48	N/A	N/A
Week 8	49 ≤ Study Day ≤ 69	N/A	N/A
Week 12	70 ≤ Study Day ≤ 97	56 ≤ Study Day ≤ 125	N/A
Week 16	98 ≤ Study Day ≤ 125	N/A	N/A
Week 20	126 ≤ Study Day ≤ 153	N/A	N/A
Week 24	Study Day ≥ 154	Study Day ≥ 126	N/A
FU Week 2	N/A	N/A	8 ≤ FU Day ≤ 20
FU Week 4	N/A	N/A	21 ≤ FU Day ≤ 30

Note: Hepatic Synthetic Function includes: ALT, AST, GGT, alkaline phosphatase, total bilirubin, direct bilirubin, albumin, INR, MELD score, CPT score, and Maddrey's DF. Lille scores will only be calculated at Weeks 1, 2, 3 and 4.

Investigator assessment of 12-lead ECG, screening lab tests, and pregnancy tests (for women of child-bearing potential) will be listed using the nominal visit. For shift tables of investigator assessment of the 12-lead ECG, if the baseline/Day 1 visit is missing, the screening value may be used in place of the baseline value. If Week 4 visit is missing, the early study drug discontinuation visit may be used in place of Week 4.

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

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

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

- In general, the baseline value will be the last nonmissing value on or prior to the first dosing date of study drug, unless specified differently. If multiple measurements occur on the same day, the last nonmissing value prior to the time of first dosing of study drug will be

considered as the baseline value (ie, for Covance laboratory values). For measurements taken on the same date with visit names of screening and baseline (ie, for vital signs and ECGs), the baseline visit value will be utilized if available. If multiple measurements occur at the same time, the average of these measurements (for continuous data) will be considered the baseline value.

- For postbaseline visits:

  — The record closest to the nominal day (nominal day for Week X = (X×7) day) for that visit will be selected.

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

  — If there is more than 1 record on the selected day, the average will be taken, unless otherwise specified.

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

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

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

4. SUBJECT DISPOSITION

4.1. Subjects Randomized and Treated and Disposition

A summary of subjects randomized and treated will be provided by treatment group and overall for each investigator within a country. The summary will present the number and percentage of subjects in the Safety Analysis Set.

A similar table will be provided by treatment group and randomization stratum. Subjects with a discrepancy in the MELD stratum (< 25 and ≥ 25) assignment in IWRS and the stratum assigned based on the screening clinical database-calculated MELD score will use the stratum assignment from the clinical database. Covance test results were used to calculate MELD scores at the screening visit for Subject IDs PPD and PPD (enrolled under protocol Amendment 1); and local laboratory tests results were used to calculate screening MELD scores for all other subjects. Subject ID PPD enrolled under Amendment 1 but used local lab results to assess entry criteria (this was a protocol violation). A listing of subjects with discrepancies in stratification assignment between IWRS and the clinical database at the time of data finalization will be provided.

The randomization schedule used for the study will be provided as a listing.

A summary of subject disposition will be provided by treatment group and overall. Study drug completion will be summarized separately for each of the 2 study drugs in the regimen. This summary will present the number of subjects screened (overall), the number of subjects randomized, and the number of subjects in each of the categories listed below.

- Safety Analysis Set / mITT (ie, randomized and treated)
- FAS (ie, randomized and treated with biopsy-proven severe AH)
- PK Analysis Set
- PK Substudy Analysis Set
- Completed Selonsertib/Placebo
- Did not complete Selonsertib/Placebo with reasons for premature discontinuation of Selonsertib/Placebo
- Completed Prednisolone
- Did not complete Prednisolone with reasons for premature discontinuation of Prednisolone
- Continuing study (if applicable)

- Completed study
- Did not complete the study with reasons for premature discontinuation of study

For the status of study drug completion (for each of the 2 drugs) 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.

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

- Subject disposition
- Reasons for screen failure (will be provided by screening ID number in ascending order) for subjects screened but not randomized to study drug
- Lot number and carton (prednisolone) or bottle (selonsertib/placebo) ID

4.2. Extent of Study Drug Exposure and Adherence

Extent of exposure to each of the individual study drugs will be examined by assessing the total duration and the level of adherence to each of the study drugs. The percentage of subjects with ≥ 80% adherence to both drugs in the regimen will be presented.

4.2.1. Duration of Exposure to Study Drug

Total duration of exposure for each individual study drug will be defined as last dosing date of individual study drug minus first dosing date of individual study drug plus 1, regardless of any temporary interruptions in study drug administration, and will be expressed in days. Days on study regimen will be the number of days that the subject was on both drugs simultaneously (ie, minimum of end dates for each of the drugs minus the start date of selonsertib/placebo plus 1). If the last study drug dosing date is missing for an individual study drug, the latest of all study drug end dates for that study drug, clinical visit date, laboratory sample collection date, or vital signs assessment date that occurred during the on-treatment period will be used. For subjects with only the month and year of last dose date, the last dose date will be set to the last day of the month (eg, Subject ID PPD

The total duration of exposure to each individual study drug and for taking both study drugs in the regimen will be summarized using descriptive statistics and using the number (ie, cumulative counts) and percentage of subjects exposed through the following time periods: Baseline (Day 1), Week 1 (Day 7), Week 2 (Day 14), Week 3 (Day 21), and Week 4 (Day 28). A 3 day window (ie, ≥ 25 days) will be used for the Week 4 category. Summaries will be provided by treatment group for the Safety Analysis Set.

4.2.2. Adherence to Study Drug

The level of protocol defined adherence to each of the 2 study drugs will be determined by the total amount of study drug administered relative to the total amount of study drug expected to be administered based on what is specified in the protocol.

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

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

Total amount of study drug administered will be the total number of pills dispensed minus the total number of pills returned. If a bottle (selonsertib/placebo) or carton (prednisolone) of study drug is not returned, the subject will be assumed to have not taken the pills.

Subjects are expected to take 28 tablets containing SEL (18 mg)/PLA and 112 tablets containing 10 mg of PRED; unless the subject is prematurely terminated from study drug due to death, lack of efficacy (meeting Lille score criteria [ie, ≥ 0.56 at Week 1 for prednisolone; or > 0.85 at Weeks 1, 2, 3, or 4 for both study drugs]), or does not have biopsy-proven severe AH on biopsy (ie, variable SDRGREAS_STD equal to 'PW', 'PV', 'LE, or 'DT' on the study drug completion eCRF for an individual study drug and subject). Subjects who were transplanted while on study drug (eg, Subject ID PPD should also only have adherence calculated to their last dose date of study drug. Note that no subjects in the study had positive results for HBsAg, HCV RNA or HIV-1/HIV-2 per central laboratory assessment which was also a criteria for calculating adherence to last dose date. Subjects who do not complete individual study drug for the reasons for premature discontinuation mentioned above--as recorded on the study drug completion form, will have adherence for that study drug calculated to last dose date of individual study drug.

In addition, subjects meeting individual SEL/PLA subject stopping criteria for the study (eg, Grade 3 or higher treatment-emergent AE that is considered to be related to study drug and results in premature discontinuation of SEL/PLA, confirmed ALT or AST > 5 x baseline, confirmed total bilirubin > 3 x baseline or nadir, or ALT or AST > 500 U/L) who prematurely discontinued SEL/PLA will have adherence for SEL/PLA calculated to their last dose date of SEL/PLA (ie, Subject ID PPD for confirmed ALT > 5 x baseline) .

Descriptive statistics for the level of on-treatment adherence to each of the 2 study drugs will be provided by treatment group for the Safety Analysis Set. The number (%) of subjects who are ≥ 80% compliant to each of the 2 study drugs will be presented.

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

4.3. Protocol Deviations

Subjects who did not meet the eligibility criteria for study entry, but were randomized into 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 Safety 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 the subject did not meet.

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

The last chronologic screening laboratory result from Covance and the screening value from the local laboratory for AST (U/L), ALT (U/L), AST/ALT ratio, total bilirubin (mg/dL), serum creatinine (mg/dL), INR, prothrombin time (PT) in seconds, PT control (seconds), calculated MELD, calculated Maddrey DF, and serology testing (HbsAg, HCV Ab, HCV RNA, HIV-1/2 Ab) will be provided. Subject IDs PPD and PPD used central laboratory values to determine eligibility (under protocol Amendment 1) while all other subjects utilized local laboratory values. Subject ID PPD enrolled under Amendment 1 and was assessed for eligibility using local labs (protocol violation).

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 age (< 50, ≥ 50 years), sex, race, and ethnicity. Age at baseline is calculated in years at the first dosing date of study drug. If a subject did not receive study drug after randomization, the subject's age will be calculated from the baseline assessment date. For screen failures, age will be calculated from the date of informed consent. The summary of demographic data will be provided for the Safety Analysis Set and for the Full Analysis Set.

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

5.2. Other Baseline Characteristics

Prior alcohol consumption (g/day) before acute AH event, weight (kg), height (cm), and BMI (kg/m^2) as a continuous and categorical (< 25, 25 to < 30 and ≥ 30 kg/m^2) variable will be summarized separately by treatment group and sex and sex overall.

Baseline characteristics for the study will include the following:

- Baseline height (cm)
- Baseline weight (kg)
- Baseline BMI (kg/m^2)
- Baseline BMI (< 25, 25 to < 30 and ≥ 30 kg/m^2)
- Prior alcohol consumption (g/day) before the acute AH event
- Alcohol Use Disorders Identification Test (AUDIT) as a continuous variable
- AUDIT as a categorical variable (< 8 [does not meet criteria]; ≥ 8 and <13 for women or <15 for men [harmful or hazardous drinking]; ≥ 13 for women, ≥ 15 for men [alcohol dependence])
- Severity of Alcohol Dependence Questionnaire (SADQ) as a continuous variable
- SADQ as a categorical variable (<16 [mild physical dependency]; 16-30 [moderate dependence]; ≥ 31 [severe alcohol dependence])
- Method of liver biopsy (percutaneous, transjugular, missing)

- Biopsy consistent with AH diagnosis (yes, no)
- Fibrosis assessment method (Metavir-equivalent, Ishak, Not Available)
- Fibrosis score as a subcategory to the fibrosis method (ie, Metavir-equivalent [F0, F1-F2, F3, F4] or Ishak [F0, F1-F2, F3-F4, and F5-F6])
- Baseline ascites (none, mild/moderate [or diuretic responsive], severe [or diuretic refractory])
- Baseline hepatic encephalopathy (none, grade 1-2 [medication controlled], grade 3-4 [medication refractory])
- Hospitalized at screening (yes, no)
- Days hospitalized prior to first dose date. Calculated as: (minimum of [date of first dose of study drug, date of release] – hospital admission date) +1 for subjects hospitalized at screening
- Baseline pyrexia (baseline temperature ≥ 38° C, ≥ 100.4° F [yes] or < 38° C, < 100.4 ° F [no])
- Baseline infection (yes, no) as recorded on the medical history eCRF.
- Treatment for baseline infection (yes, no) as recorded on the medical history eCRF
- Evidence of baseline infection on chest X-ray (yes, no)
- Baseline MELD score (as a continuous variable)
- Baseline CPT score (as a continuous variable)
- Baseline CPT class (A [scores of 5-6], B [scores of 7-9], C [scores of 10-15])
- Baseline Maddrey DF score (as a continuous variable)
- Baseline AST (U/L)
- Baseline ALT (U/L)
- Baseline AST/ALT Ratio
- Baseline total bilirubin (mg/dL)
- Baseline direct bilirubin (mg/dL)
- Baseline GGT (U/L)

- Baseline albumin (g/dL)
- Baseline alkaline phosphatase (U/L)
- Baseline INR
- Baseline serum creatinine (mg/dL)

Alcohol Consumption Level and Alcohol Dependence

The ***Alcohol Use Disorders Identification Test (AUDIT)*** is a screening tool developed by the World Health Organization (WHO) to assess alcohol consumption, drinking behaviors, and alcohol-related problems. AUDIT is comprised of 10 questions, with scores for each question ranging from 0 to 4. The total score (sum of a subject's scores across each of the 10 individual questions) for AUDIT will be summarized as a continuous variable and for the categories: < 8 (does not meet criteria); ≥ 8 and <13 for women or <15 for men (harmful or hazardous drinking) or ≥ 13 for women, ≥ 15 for men (alcohol dependence).

The ***Severity of Alcohol Dependence Questionnaire (SADQ)*** is a short, self-administered, 20-item questionnaire developed by the Addiction Research Unit at the Maudsley Hospital to measure severity of dependence on alcohol. Each question is assigned a score based on the subjects response (0 [almost never/not at all], 1 [sometimes/slightly], 2 [often/moderately], or 3 [nearly always/quite a lot]). Total score (sum of scores for the subject across the 20 questions) for SADQ will be summarized as a continuous variable and for the categories: <16 (mild physical dependency); 16-30 (moderate dependence); ≥ 31 (severe alcohol dependence).

Formulas for MELD, CPT, and Maddrey's DF

Clinical assessments for ascites and hepatic encephalopathy (to calculate CPT scores) and the Covance laboratory collection dates for each laboratory test required for MELD and CPT scores are recorded on the CPC_MELD eCRF. Formulas for calculation of MELD score, CPT score, and Maddrey's DF are described in Section 6.2.8 of this SAP.

Baseline disease 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. Summaries of baseline characteristics will be provided for the Safety Analysis Set and Full Analysis Set.

No formal statistical testing is planned.

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

5.3. Prior Corticosteroids for Treatment of Alcoholic Hepatitis

Corticosteroids could be administered for ≤ 3 days prior to starting study drug per protocol. Medications with ATC class level 2 = "Corticosteroids for systemic use" that started on Study

Days -3, -2, or -1 and stopped on Study Day -1 or 1 will be included. Subject ID PPD started Urbason on Study Day -7 (protocol violation) and is included in the listing and summary table. The indication for the drug entered on the CM eCRF will be checked to ensure that it is consistent with administration for an indication of alcoholic hepatitis. Corticosteroids used to treat alcoholic hepatitis prior to starting study drug will be summarized by preferred drug name.

Prior corticosteroid medications used to treat AH will be provided in a by-subject listing sorted by subject ID number and administration date in chronological order.

5.4. Medical History and Baseline Infections

General medical history data will be collected at screening and listed only. General medical history data will not be coded. Subjects with baseline infections will have a checkbox marked on the MH eCRF to denote baseline infection events, and baseline infections will be listed separately. Results from cultures, x-rays, and ascitic fluid neutrophil cell counts (ie, > 250 cells/mm^3) for spontaneous bacterial peritonitis (SBP) confirming reported infections during the screening period will be included on this listing.

Prior medications that were used to treat baseline infections will be identified as drugs with a pull down indication of "infection" on the CM eCRF. Medications with an end date prior to screening date or a start date that is after the first dosing date of SEL/PLA will be excluded.

Listings will be provided for chest X-rays, and liver imaging performed at the screening visit.

6. EFFICACY ANALYSES

The primary efficacy analysis will include subjects in the FAS. A secondary analysis of efficacy will include subjects in the mITT analysis set. Subjects who receive a liver transplantation while enrolled in the study will have measurements collected up to the time of liver transplantation included in efficacy analyses; data collected after transplantation will be excluded from efficacy analyses.

6.1. Secondary Efficacy Endpoints:

- Number (%) of subjects who die by Study Day 28 and by Weeks 8, 12, and 24
- Number (%) of subjects receiving a liver transplant by Study Day 28 and by Weeks 8, 12, and 24
- Summary of Lille score by visit through Week 4
- Number (%) of subjects with Lille response (score < 0.45) at Day 7 (eg, Week 1)
- Number (%) of subjects with Lille null response (score ≥ 0.56) at Day 7 (eg, Week 1)
- Mortality Risk at Months 2 and 6 based on Lille score response at Day 7 (eg, Week 1) and the baseline MELD score (continuous)
- Number (%) of subjects with infection while on study
- Number (%) of subjects with HRS while on study
- Length of initial hospital stay
- Change from baseline in liver biochemistry tests (ALT, AST, GGT, albumin, alkaline phosphatase, total bilirubin, direct bilirubin, and INR) by analysis visit through Week 24
- Change from baseline in prognostic indices (MELD, CPT, and Maddrey's DF) by analysis visit through Week 24

6.2. Analysis Methods for Secondary Efficacy Endpoints

6.2.1. Death

The number (%) of subjects with a death by Study Day 28, and by Weeks 8, 12, and 24 will be displayed by treatment group. For the endpoint death by Day 28, subjects who die on/prior to Study Day 28 or are known to be alive through Study Day 28 will be included in the denominator for calculation of percentage of subjects with death. Subjects not followed through Day 28 will be summarized by their reason for premature discontinuation from study. A 2-sided

Fisher's exact test will be used to explore whether there are differences between treatment groups in percentage of subjects with death by Day 28. Deaths by Weeks 8, 12, and 24 will be summarized in the same manner as deaths by Study Day 28. Kaplan-Meier estimates of survival and the 95% CI (based on Greenwood's formula and the log-log transformation of the survival function) will also be presented at each timepoint. A Kaplan-Meier figure for survival will be displayed. Deaths will be recorded on the Death and/or survival status eCRF and the date of last subject follow-up will be determined from the maximum of eCRF visit dates (including subject survival status visit dates), and Covance laboratory collection dates.

A listing of subject deaths while on study will be provided for the mITT analysis set; subjects included in the FAS will be flagged. Days from first dose of study drug (ie, Study Day) and days from last dose of study drug (ie, Follow-up Day) for subjects for whom death occurs after stopping study drug, will be provided in the listing.

6.2.2. Liver Transplantation

The number (%) of subjects with liver transplantation by Study Day 28, and by Weeks 8, 12, and 24 will be displayed by treatment group. For the endpoint liver transplantation by Day 28, subjects undergoing liver transplantation by Study Day 28 or who are known to still be on study through Day 28 will be included in the denominator for calculation of percentage of subjects with liver transplantation. Subjects not followed through Day 28 will be summarized by their reason for premature discontinuation from study. Liver transplantation by Weeks 8, 12, and 24 will be summarized in a similar manner. Liver transplants will be recorded on the survival status eCRF.

A listing of liver transplants while on study will be provided for the mITT analysis set; subjects included in the FAS will be flagged. Days from first dose of study drug (ie, Study Day) and days from last dose of study drug (ie, Follow-up Day) for those transplanted after stopping study drug will be provided in the listing.

6.2.3. Transplantation-free survival

Time up to the first liver transplant or death event (in days) will be calculated as:

(first of date of liver transplant/death – randomization date + 1)

Data from surviving subjects with no transplant will be censored at the last date that the subject is known to be alive and transplant-free (maximum of central laboratory dates and eCRF [including survival status] visit dates).

In the following SAS code, *Days* is the number of days from randomization date to the first death/liver transplant or to the date of last study visit if no death or liver transplant has been observed. *Status* is a binary variable with 1 representing no death and no transplant observed and 0 representing that there is a death or transplant that has been observed.

```
proc lifetest data=txfs_2groups timelist= 28 56 84 168 conftype=loglog alpha=0.05 ;
    Time Days*Status(1);
    Strata = trtgrp;
run;
```

For each treatment group, the Kaplan-Meier (KM) estimates of transplant-free survival at Day 28, and at Weeks 8, 12, and 24 and the 95% CI will be provided. The 95% CI will be calculated based on Greenwood's formula and log-log transformation of the survival function.

A figure of the KM curve for transplant-free survival will be provided.

The median, Q1 and Q3 of the transplant-free survival will be provided for each treatment group. The 95% CI for median transplant-free survival is based on Brookmeyer-Crowley method of inverting a generalization of the sign test for censored data will also be provided for each treatment group.

6.2.4. Lille score

The Lille score is a tool that has historically been used to predict which subjects with severe AH (eg, screening Maddrey DF score ≥ 32) are not responding to corticosteroid therapy; usually after Study Day 7, and are potential candidates for alternative therapies {Louvet 2007}. The Lille score is calculated using baseline factors: age, albumin, total bilirubin, serum creatinine, prothrombin time; and the change in total bilirubin between baseline and Day 7 according to the following formula:

Lille score = Exp(-R)/[1+exp(-R)], where
R = (3.19 – (0.101 × age [yrs]) + (1.47 × BL albumin [g/dL]) +
(0.28215 × (BL total bilirubin [mg/dL] – Day 7 total bilirubin [mg/dL])) –
(0.206 × RENAL INSUFFICIENCY) - (0.11115 × BL total bilirubin [mg/dL]) –
(0.0096 × BL prothrombin time [seconds])

Renal insufficiency is rated 0 if absent and 1 if present (serum creatinine ≤ 1.3 or > 1.3 mg/dL, respectively). The result will be rounded to the nearest 0.001. Covance central laboratory data will be used to calculate Lille scores for a subject for analysis purposes except when 1 or more of the central values required to calculate the Lille score at Week 1 are missing and local laboratory data is available to calculate a Week 1 score. For these cases, local labs will be used to calculate all Lille scores for the subject. See Section 3.6.1 of this SAP for a complete description of imputations for Lille score for subjects in whom a Week 1 Lille score cannot be calculated based on central laboratory data.

Lille score will be summarized as a continuous variable by treatment group and visit at Weeks 1, 2, 3, and 4 by selecting the total bilirubin value for the subject and visit using the analysis visit windows specified in Section 3.8.2 of this SAP. An additional timepoint will be displayed for "Week 4 or last observation carried forward (LOCF)". For this additional timepoint, a subject will be included with their Week 4 analysis visit Lille score, or with the last chronologic Lille score collected between Study Days 2 and 24 for those subjects who have a missing Week 4 Lille score. The total bilirubin for the visit window will be substituted in place of the Day 7 total bilirubin value in the Lille score formula above to calculate the Lille score for Weeks 2, 3, and 4. The median (Q1, Q3) Lille score value at each on-treatment visit will be provided as a figure.

Lille score will additionally be summarized as a categorical variable at Week 1, Week 2, and at Week 4 (LOCF) by treatment group and visit for the following:

1) The number and percentage of subjects with a Lille response, defined as a Lille score < 0.45 (yes or no)

2) The number and percentage of subjects with a Lille null response, defined as a Lille score ≥ 0.56, will be displayed by treatment group and visit. Null response is used as a criteria for premature discontinuation of prednisolone in clinical practice. Subjects with a complete or partial response (Lille score < 0.56) will be further subdivided into complete responders (Lille score < 0.16) and partial responders (Lille score 0.16 to < 0.56).

The denominator for the percentage calculation will be the number of subjects in the treatment group for the FAS or mITT analysis set (as appropriate). Subjects missing a Lille score value within the visit window will be counted as failures. Subjects with a calculated Lille score meeting non-responder or null-responder criteria will be summarized as "observed" failures. Subjects missing a value within the visit window will be summarized as "missing value". The reasons for subjects not having a Lille score will be summarized at each visit as follows:

1) Subjects who discontinue both study drugs in the regimen prior to the target day (ie, Study Days 7 [Week 1 and Week 4 LOCF] and Day 14 [Week 2] for the visit window will be summarized by the premature discontinuation reason for SEL/PLA from the study drug completion eCRF.

2) Subjects ongoing at the time of the visit will be summarize as "missing value at visit"

For the endpoints Lille response (yes, no) and Lille null response (vs. complete or partial response), p-values from a 2-sided Fisher's exact test will be presented for the Week 1 visit to explore whether there are differences between treatment groups.

A listing of the Lille scores included in analysis will be provided. A footnote will provide Subject IDs for those subjects who had Lille scores calculated using local laboratory data.

6.2.5. Mortality Risk using Baseline MELD score and Lille Score at Day 7

A scoring system combining the Lille score at Day 7 and the baseline MELD score to calculate the 2- and 6-month overall mortality risk was created, and tested with a secondary derivation dataset (ie, validation dataset) {Louvet 2015}. The steps for calculating the mortality risk for an individual subject are described below:

Step 1: Calculate the mortality probability for an individual subject using the Lille score at Week 1 and baseline MELD scores from central laboratory data. Subjects with a missing centrally-assessed Lille score at Week 1 or baseline MELD score will utilize imputed values based on local laboratory data as specified in Section 3.6.1 of this SAP.

$S = [2.4778 \times (\text{Week 1 Lille score} - 0.4114) + 0.0695 \times (\text{Baseline MELD} - 24.6812)] \times 0.9836$

where,

1) 0.4114 = mean value of Lille model in the secondary derivation dataset

2) 24.6812 = mean value of MELD score in the secondary derivation dataset

3) 0.9836 = the shrinkage factor estimated using bootstrap validation in the secondary derivation dataset

4) 2.4778 and 0.0695 = regression coefficients calculated from the multivariable prognostic model for the secondary derivation dataset

Step 2: Calculate mortality risk using S:

2-month mortality risk = $[1-(0.8239^{\exp(S)})]*100$

6-month mortality risk = $[1-(0.7285^{\exp(S)})]*100$

Where 0.8239 and 0.7285 were the survival rate at the mean values of predictors in secondary derivation dataset (calculated as the pooled survival estimates from cohorts included in secondary derivation dataset).

Numerical Example: a subject with Week 1 Lille score = 0.45 and a baseline MELD = 21:

Step 1: Calculate $S = [2.4778 \times (0.45 - 0.4114) + 0.0695 \times (21 - 24.6812)] \times 0.9836 = -0.1576$

Step 2: Calculate the mortality risk using S

2-month mortality risk = $[1-(0.8239^{\exp(-0.1576)})]*100 = 15.3\%$

6-month mortality risk = $[1-(0.7285^{\exp(-0.1576)})]*100 = 23.7\%$

Mortality risk at Month 2 and at Month 6 will be provided as a continuous variable by treatment group.

6.2.6. Length of Initial Hospital Stay

The number and percentage of subjects who were hospitalized at the time they were screened for the study will be presented by treatment group. The denominator for percentage will be the number of subjects in the FAS or modified ITT analysis set (as appropriate).

For those hospitalized at the time they were screened for the study, the following will be presented (denominator for percentage will be number hospitalized in appropriate analysis set):

- Number and percentage of subjects who were transferred from another hospital to the current hospital where they are participating in this study
- Number of subjects who were released from the hospital after the screening visit and prior to first dose of SEL/PLA study drug
- Number and percentage of subjects still in the hospital on Study Day 1.

  In addition, for those still in the hospital on Study Day 1, summary statistics of days hospitalized from date of first dose of SEL/PLA by treatment group and death status (eg., alive or dead) will be presented where

  Days hospitalized from first dose of SEL/PLA =

  (Date of release from hospital – date of first dose of SEL/PLA +1)

If the death date is the same as the release date or the subject has a nonmissing death date and there is no release date from hospitalization, the subject will be assumed to be "dead" upon release from the hospital. Date of death will be substituted for date of release in the formula for days hospitalized from first dose of SEL/PLA.

6.2.7. Events of Interest

The number and percentage of subjects with the following 2 types of events will be summarized:

- Infections of Interest (as described in Section 6.9.9 of the study protocol)
- Hepatorenal Syndrome events (meeting International Ascites Club criteria as described in Section 6.9.8 of the study protocol)

A postbaseline infection of interest will be considered to be "definite" in subjects with clinical evidence of infection (ie, AE with the infection field marked 'yes' on the AE eCRF) and a positive culture from a normally sterile source; infiltrate on chest x-ray and treatment with antibiotics; or ascitic fluid neutrophils ≥ 250 cells/mm^3, regardless of culture positivity for SBP. All other infections will be considered to be "probable". Results from laboratory investigations

will be used to enter the most specific AE verbatim term possible for coding purposes (ie, "***E. Coli*** urinary tract infection" for a urinary tract infection where the pathogen "***E. Coli***" was present in a urine culture); and to serve as source documentation of the methods used to determine that the infection was "definite".

A summary of postbaseline "infections" (ie, adverse events that have 'yes' marked for infection on the AE eCRF) will be presented by treatment group, high level group term (HLGT) and lower lever term (LLT) from the MedDRA dictionary separately for infections that are "definite" infections and for those that are "definite/probable" infections. Multiple events reported within a HLGT, and LLT will be counted once only per subject in each summary. Infections will be summarized in alphabetic order of HLGT and then by LLT in descending total frequency within each HLGT. Infections with postbaseline onset dates or worsening on or after the first dose date of study drug through end of study will be summarized.

Culture and x-ray results collected for documenting definite infections will be presented alongside the reported infection in a listing sorted by start date for the infection and procedure date for the culture/x-ray. Cultures collected on/after Study Day 1 will be listed.

Postbaseline medications used to treat infections (identified from an indication of "Infection" on the CM eCRF) will be summarized by treatment group and preferred name. Medications with stop dates prior to first dose date of SEL/PLA will be excluded.

A listing of subjects with HRS events entered on the AE eCRF that meet International Ascites Club criteria as described in Section 6.9.8 of the study protocol will be provided. Subjects with an AE preferred term of "Hepatorenal syndrome" from the AE eCRF will be screened by the medical monitor to determine whether the event meets Ascites Club HRS criteria. New or worsening postbaseline HRS events reported during the study will be summarized.

Medications used to treat HRS (ie, those with an indication of 'HRS' on the concomitant medication eCRF) will be summarized by treatment group and preferred name. Medications with stop dates prior to first dose date SEL/PLA will be excluded from analyses. Medications used to treat HRS will be listed.

6.2.8. Liver Biochemistry and Prognostic Indices

Summary statistics for the absolute value and change and percentage change from baseline for liver biochemistry tests (ALT, AST, GGT, albumin, alkaline phosphatase, total bilirubin, direct bilirubin, and INR) and prognostic indices (MELD, CPT and Maddrey's DF) will be presented by visit through Week 24 using central laboratory data except when noted otherwise (see Section 3.8.2 of the SAP for visit windows; and Section 3.6.1 for baseline MELD imputation rule when central laboratory data is not available).

Percentage change from baseline is calculated as:

([score at visit – score at baseline] ÷ score at baseline) × 100

An additional timepoint will be added for "Week 4 (LOCF)". For this additional timepoint, a subject will be included with their Week 4 value, or with the last chronologic value collected between Study Days 2 and 24 for subjects who are missing a Week 4 value. For all liver biochemistry tests and prognostic scores, subjects who receive a liver transplant while on study will have measurements collected up to the date of transplant included for summary tables.

Median (Q1, Q3) absolute values by visit will be plotted for MELD score, ALT, AST, total bilirubin and INR throughWeek 24 for the final analysis. Median (Q1, Q3) change and percentage change from baseline by visit will be plotted for MELD score and for total bilirubin.

A listing of values included in efficacy analyses will be provided with subjects included in the FAS flagged in listings.

Formulas for calculating each of the prognostic indices are described below:

Maddrey DF score =
[4.6 × (PT subject [sec] – PT control [sec])] + total bilirubin (mg/dL)

Note: PT control [sec] is only available at the screening visit for each subject. For calculations over time, the subject's screening PT control [sec] will be used to calculate scores at each of the visits.

MELD score =
$10 \times \{[0.957 \times \text{Ln}(\text{Scr})] + [0.378 \times \text{Ln}(\text{Tbil})] + [1.12 \times \text{Ln}(\text{INR})] + 0.643)\}$,

where Scr = serum creatinine (in mg/dL), Tbil = Total Bilirubin (in mg/dL), INR = international normalized ratio, and Ln = natural log. If any lab value is less than 1.0, then it will be set to 1.0 in the calculation. If the subject received dialysis at least twice in the past week, or if serum creatinine is > 4.0 mg/dL, then Scr will be set to 4.0 mg/dL in the above formula. The result will be rounded to the nearest whole number. Subjects missing a baseline MELD score using central laboratory data will have their baseline MELD score imputed as described in Section 3.6.1 of this SAP.

CPT score = Sum of the scores related to the 5 parameters below for a given subject and study visit (if any of the components are missing, the score will not be calculated for that subject and visit):

Parameter	POINTS		
	1	2	3
Encephalopathy	None	Grade 1-2 (medication controlled)	Grade 3-4 (medication refractory)
Ascites	None	Mild/Moderate (diuretic responsive)	Severe (diuretic refractory)
Bilirubin (mg/dL)	< 2	2 - 3	> 3
Albumin (g/dL)	> 3.5	2.8 - 3.5	< 2.8
INR	< 1.7	1.7 - 2.3	> 2.3

Note: if either ascites or encephalopathy is "none" because the subject is taking medication which has controlled the symptoms, the scoring should be 2 points (not 1 point).

The CPT score is obtained by adding the points for each parameter for a given subject at a visit. The CPT class is assigned based on the score: CPT A (5-6 points), CPT B (7-9 points), CPT C (10-15 points).

For the MELD and CPT calculations, the dates for each of the individual laboratory tests utilized in the formula are collected on the CPC_MELD eCRF and merged with the Covance laboratory dataset by laboratory test and laboratory collection date prior to calculating the scores. The visit date for the CPC_MELD eCRF determines the study day for purposes of determining the analysis visit windows as specified in Section 3.8.2 of this SAP.

6.3. Exploratory Efficacy Endpoints

PPD

6.4. Analysis methods for Exploratory Efficacy Endpoints

PPD

6.5. Changes to Efficacy Analysis

Analyses of the endpoints change from baseline in LOXL2, CK18, serum cytokines and metabolic profiles, LPS, procalcitonin, and ASK-1 pathways will be described in a separate biomarker analysis plan (BAP).

Fasting lipid tests (total cholesterol, HDL, LDL, VLDL), and triglycerides will not be summarized as exploratory efficacy endpoints as the requirement for fasting was removed in Amendment 2 of the protocol. In addition, Covance laboratories does not report results for cholesterol values when the sample is "icteric". As a high percentage of subjects have total bilirubin levels > 10 mg/dL for this subject population, these analyses would exclude the most severe AH subjects, and would not be representative of the entire set of subjects. The lipid profile will be summarized for safety only and insulin levels will be listed only using the same visit windows used for HbA1c.

It should also be noted that many GGT and total protein values were cancelled by Covance due to icteric samples (ie, high total bilirubin). Summaries will be presented for completeness, but it should be noted that many values, especially those at early timepoints, will be missing.

Analysis of the Chronic Liver Disease Questionnaire (CLDQ) will not be performed for the final analysis since there was no evidence of improved efficacy with treatment of SEL + PRED vs. PLA + PRED when the primary analysis was performed.

7. SAFETY ANALYSES

7.1. Adverse Events and Deaths

7.1.1. Adverse Event Dictionary

Clinical and laboratory adverse events (AEs) will be coded using the current version of MedDRA. System organ class (SOC), 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 Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. The severity grade of events for which the investigator did not record severity will be categorized as "missing" for tabular summaries and data listings, and the most severe event will be considered in data presentations.

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." Events for which the investigator did not record relationship to study drug will be considered related to study drug for summary purposes. However, by-subject data listings will show the relationship as missing.

7.1.4. Serious Adverse Events

Serious adverse events (SAEs) will be identified and captured as SAEs if AEs meet the definition of an SAE specified in the study protocol. SAEs captured and stored in the clinical database will be reconciled with the SAE database from the Gilead Pharmacovigilence 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 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 any study drug

An AE with completely missing onset and stop dates, or with the onset date missing and a stop date later than the first 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 AEs will be provided by treatment group and will present the number and percentage of subjects who had the following: any TEAE, any TEAE of Grade 2 or higher, any TEAE of Grade 3 or higher (further broken down by highest grade reported per subject [ie, Grade 3, 4, 5]), any TE treatment-related AE, any TE treatment-related AE of Grade 2 or higher, any TE treatment-related AE of Grade 3 or higher (further broken down by highest grade reported per subject [ie, Grade 3, 4, 5]), any TE SAE, any TE treatment-related SAE, any TEAE that led to premature discontinuation of both study drugs (defined as ≥ 1 AE with action taken on SEL/PLA='study drug withdrawn' and ≥ 1 AE with action taken on PRED='study drug withdrawn'), any TEAE that led to premature discontinuation of Selonsertib/Placebo, any AE that led to premature discontinuation of Prednisolone, any TEAE that led to dose reduction or interruption of Prednisolone, any TEAE that led to interruption of Selonsertib/Placebo, any TEAE that led to interruption of Prednisolone, any TEAE that led to premature discontinuation from study, and all deaths reported during the study will also be summarized and included in this table.

The number and percentage of subjects will be provided and summarized by treatment group, SOC and PT for the following:

- All TEAEs
- 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 SAEs
- All TE treatment-related SAEs
- All TEAEs leading to temporary interruption of Selonsertib/Placebo
- All TEAEs leading to temporary interruption of Prednisolone
- All TEAEs leading to dose modification or temporary interruption of Prednisolone
- TEAEs leading to premature discontinuation of Selonsertib/Placebo
- TEAEs leading to premature discontinuation of Prednisolone
- TEAEs leading to discontinuation of both drugs in the study regimen (defined as AEs that led to discontinuation of either study drug for subjects with ≥ 1 AE with action taken on SEL/PLA=study drug withdrawn and ≥ 1 AE with action taken on PRED=study drug withdrawn)
- All AEs recorded between screening and prior to first dose of study drug
- All SAEs with an outcome of death

Multiple events reported within an SOC or PT will be counted once only per subject in each summary. Adverse events will be summarized by treatment group and will be listed first in alphabetic order of SOC and then by PT in descending total frequency within each SOC. In summaries by severity grade, the most severe grade will be used for those AEs that occurred more than once in an individual subject during the study.

In addition to the above summary tables, the following AEs will be summarized by treatment group and PT only:

- All TEAEs (occurring in ≥ 10% of subjects within any group)
- TE treatment-related AEs (occurring in ≥ 5% of subjects within any group)
- Grade 3 or Higher TE AEs
- Grade 3 or Higher TE treatment-related AEs

- Grade 3 or Higher TE treatment-related AEs Leading to Premature Discontinuation of Selonsertib/Placebo
- TE SAEs
- TE treatment-related SAEs

The sort order for these tables will be in descending order of total frequency of PT events and alphabetic order of PT for events with the same total frequency.

At the request of the Pharmacovigilence and Epidemiology group, the following AE tables will be produced to summarize by treatment group, SOC, HLT and PT:

- All TE AEs
- TE SAEs

The sort order for these tables will be in descending order of total frequency of HLT and PT events and alphabetic order for SOC.

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
- All AEs of Grade 3 or higher related to study treatment
- SAEs
- SAEs related to study treatment
- Deaths
- All AEs leading to death
- AEs leading to discontinuation of any of the study drugs
- AEs leading to dose modification or interruption of any of the study drugs

7.1.7. Analysis of Adverse Events of Interest

Post-baseline criteria (up to last dose date of SEL/PLA [confirmatory values may be collected after the last dose date]) will be used to screen for individual subjects who should stop dosing with SEL/PLA study drug. DMC members used these same criteria to determine whether there was a > 20% higher percentage of subjects in the SEL + PRED group than PLA + PRED group with events in any of the 4 categories (ie, DMC trial stopping criteria).

SEL/PLA study drug stopping criteria for an individual subject is as follows:

1) Grade 3 or higher, treatment-emergent, treatment-related adverse event(s) of a specific type (excluding evaluation of liver function) that leads to discontinuation of SEL/PLA

2) Death on/prior to Study Day 28

3) Lille Score > 0.85 while on study drug

4) Any of the post-baseline SEL/PLA laboratory stopping criteria:

   - ALT or AST > 500 U/L
   - ALT or AST > 5 x Baseline/Day 1 (confirmed on repeat testing)
   - Total Bilirubin > 3 x Baseline/Day 1 or Nadir (confirmed on repeat testing)

The baseline/Day 1 value will be defined as the last available measurement on/prior to first dose of SEL/PLA, and the nadir value will be defined as the lowest postbaseline value prior to the current value being assessed. A listing will be provided that includes each individual subject who met any of the SEL/PLA stopping criteria.

Prednisolone study drug stopping criteria in an individual subject is as follows: Subjects with a Week 1 Lille score ≥ 0.56 will be prematurely discontinued from PRED. This criteria is the same as the secondary efficacy parameter Lille null response (Lille score ≥ 0.56 at Week 1) which is described in Section 6.2.4 of this SAP.

7.2. Laboratory Evaluations

Summaries of laboratory data will be provided for the Safety Analysis Set and will include data collected up to the date of last dose of any study drug plus 30 days for subjects who have permanently discontinued study drug. 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 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 and analysis visit in chronological order for screening tests, hematology, serum chemistry, and coagulation, separately. Values falling outside of the relevant reference range and/or having a severity grade of 1 or higher according to CTCAE toxicity grading will be flagged in the data listings, as appropriate.

No formal statistical testing is planned.

Special handling of central laboratory serum creatinine data:

At initiation of the study, the Covance Statement of Work (SOW) specified that serum creatinine be analyzed using the Jaffe method with a reflex to serum enzymatic creatinine. Early in the

study, high bilirubin values prohibited resulting of creatinine, so the SOW was updated to use serum enzymatic creatinine with a reflex to LCMSMS methodology if serum enzymatic creatinine could not be resulted; Jaffe method was no longer used. At the same time, Gilead asked Covance to perform regression analysis to determine if data from serum enzymatic creatinine and LCMSMS methods were combinable. Fourty samples (not from this study) measured creatinine using all 3 methods (Jaffe, enzymatic serum creatinine, and LCMSMS), and regression analysis using Deming and regular regression was performed.

Results of previous regression analyses comparing the Jaffe method and serum enzymatic creatinine met Covance's criteria for combinability of data using the 2 methods (ie, 95% CI on slope contains 1; and 95% CI on intercept contains 0). Regression analysis of the 40 samples for LCMSMS and the Jaffe methods came close to meeting the combinability criteria, and only 4 samples from Study GS-US-416-2124 were analyzed using the Jaffe method. LCMSMS and serum enzymatic creatinine failed to pass the combinability criteria (95% CI on the slope contained 1; but 95% CI on the intercept did not contain 0). Examination of individual data points as well as the reported bias (-0.055 mg/dL) show that serum LCMSMS was reading out approximately .055 mg/dL lower than serum enzymatic creatinine across the range of values.

In order to combine creatinine data from the 3 different test methods, Gilead will create a new lab test code called "GSI Serum Creatinine" that combines data from the 3 serum creatinine methods for analysis---adjusting for the LCMSMS negative bias (by adding 0.06 mg/dL [for 2-decimal place reporting] to the reported result). Covance has recommended using Jaffe normal ranges for serum creatinine LCMSMS, and results from prior regression analysis suggest that serum enzymatic creatinine is combinable with the Jaffe method. Results of the "GSI serum creatinine" lab test code will be toxicity graded using CTCAE Version 4.03 and the Jaffe method normal ranges.

7.2.1. Summaries of Numeric Laboratory Results

Descriptive statistics will be provided by treatment group for hemoglobin, hematocrit, lymphocytes, neutrophils, platelet count, white blood cells (WBCs), bicarbonate, sodium, chloride, magnesium, phosphorus, potassium, albumin-corrected calcium, lactate dehydrogenase, blood urea nitrogen, serum creatinine, and serum glucose as follows:

- Baseline values
- Values at each postbaseline analysis visit
- Change from baseline at each postbaseline analysis visit

A baseline laboratory value will be defined as the last measurement obtained on or prior to the date of first dose of study drug. Change from baseline to a postbaseline visit will be defined as the value at the visit minus the baseline value. The mean, SD, median, Q1, Q3, minimum, and maximum values will be displayed to the reported number of digits; SD values will be displayed to the reported number of digits plus 1.

Median (Q1, Q3) serum creatinine value over time will be plotted.

In the case of multiple values in an analysis window, data will be selected for analysis as described in Section 3.8.3.

7.2.2. Graded Laboratory Values

The CTCAE Version 4.03 will be used for assigning toxicity grades (0 to 4) to laboratory results for analysis. Grade 0 includes all values that do not meet the criteria for an abnormality of at least Grade 1. For laboratory tests with criteria for both increased and decreased levels, analyses for each direction (ie, increased, decreased) will be presented separately.

7.2.2.1. Treatment-Emergent Laboratory Abnormalities

Treatment-emergent laboratory abnormalities are defined as values that increase at least 1 toxicity grade from baseline at any postbaseline time point, up to and including the date of last dose of study drug plus 30 days for subjects who permanently discontinued study drug. If the relevant baseline laboratory value is missing, any abnormality of at least Grade 1 observed within the time frame specified above will be considered treatment emergent.

7.2.2.2. Treatment-Emergent Marked Laboratory Abnormalities

Treatment-emergent marked laboratory abnormalities are defined as values that increase from baseline by at least 3 toxicity grades at any postbaseline time point, up to and including the date of the last dose of study drug plus 30 days for subjects who permanently discontinued study drug. 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

The following summaries (number and percentage of subjects) for treatment-emergent laboratory abnormalities will be provided by laboratory test (and direction of abnormality, when applicable) and treatment group; subjects will be categorized according to the most severe postbaseline abnormality grade for a given lab test:

- 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 time point 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 toxicity grades displayed.

7.3. Body Weight, Height, BMI and Vital Signs

Descriptive statistics will be provided by treatment group for systolic and diastolic blood pressure, and pulse as follows:

- Baseline value
- Values at each postbaseline analysis visit
- Change from baseline at each postbaseline analysis visit

A baseline value will be defined as the last available value collected on or prior to the date of first dose of study drug. For subjects with screening and baseline visits conducted on the same date (ie, Subject ID PPD the baseline record will be utilized as the baseline value. Change from baseline to a postbaseline visit will be defined as the postbaseline value minus the baseline value.

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 height, body weight, BMI, and vital signs will be provided by subject ID number and time point in chronological order.

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. Concomitant Medications

Concomitant medications are defined as medications taken while the subject is taking 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 descending overall frequency of preferred name. For drugs with the same frequency, sorting will be done alphabetically for preferred name.

For the purposes of analysis, medications with a stop date that is on or prior to the date of first dosing date of study drug or a start date that is 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.

Summaries will be based on the Safety Analysis Set. No formal statistical testing is planned.

All prior and concomitant medications will be provided in a by-subject listing sorted by subject ID number and administration date in chronological order.

7.4.2. Concomitant Enteral and Parenteral Nutrition Medications

Enteral and parenteral nutrition medications will be summarized separately using similar rules to those used for concomitant medications. Enteral and parenteral nutrition products are defined as medications recorded on the CM eCRF with a pull-down menu indication of "Parenteral or Enteral Nutrition". A summary of concomitant enteral and parenteral nutrition medications will be based on the Safety Analysis Set.

All enteral and parenteral nutrition medications 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 investigator assessment of a subject's ECG results at Week 4/early study drug discontinuation visit and Week 8 compared with their baseline value will be presented by treatment group using the following categories: normal; abnormal, not clinically significant; abnormal, clinically significant; or missing. A subject with a missing ECG result at Baseline/Day 1 will have the screening visit used for the baseline value. 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 nominal visit in chronological order.

7.6. Other Safety Measures

A listing of pregnancies (or a listing stating that none were observed) will be provided.

7.7. Changes From Protocol-Specified Safety Analyses

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

8. PHARMACOKINETIC ANALYSES

8.1. PK Sample Collection

A single PK sample will be collected on Day 1 (2 ± 1 hour postdose), at Week 1 (24 ± 4 hours postdose), Week 2 (2 ± 1 hour and 24 ± 4 hours postdose), and Week 4 (24 ± 4 hours postdose).

PPD

A population PK model may be developed to characterize the PK of selonsertib and its metabolites (as applicable). Data from this study (single PK and PK substudy) may be combined with data from other studies in a meta-population analysis using nonlinear mixed-effects modeling techniques. Details of the population PK analysis will be provided in a separate population PK analysis plan.

8.2. PK Analyses Related to Intensive PK Sampling

Steady-state PK over a 24 hour dosing interval will be determined in subjects in the PK Substudy analysis set. Concentrations of selonsertib and GS-607509 in plasma will be determined using validated bioanalytical assays.

8.2.1. Estimation of Pharmacokinetic Parameters

Pharmacokinetic (PK) parameters will be estimated by application of a nonlinear model (using Phoenix WinNonlin® software version 6.3) using standard noncompartmental methods. The linear up/log down trapezoidal rule will be used in conjunction with the appropriate noncompartmental model, with input values for dose level, dosing time, plasma concentration, and corresponding real-time values, based on drug dosing times whenever possible.

All predose sample times before time-zero will be converted to 0. For area under the curve (AUC), samples BLQ of the bioanalytical assays occurring prior to the achievement of the first quantifiable concentration will be assigned a concentration value of 0 to prevent overestimation of the initial AUC. Samples that are BLQ at all other time points will be treated as missing data in WinNonlin. The nominal time point for a key event or dosing interval (τ) may be used to permit direct calculation of AUC over specific time intervals. The appropriateness of this approach will be assessed by the PK scientist on a profile-by-profile basis.

Pharmacokinetic parameters such as AUC_{tau}, λ_z and $t_{1/2}$ are dependent on an accurate estimation of the terminal elimination phase of drug. The appropriateness of calculating these parameters will be evaluated upon inspection of PK data on a profile-by-profile basis by the PK scientist.

8.2.2. Pharmacokinetic Parameters

The pharmacokinetic parameters for selonsertib and GS-607509 will be computed for all subjects with evaluable PK profiles who were in the selonsertib + prednisolone group. For each subject, the following PK parameters will be calculated for selonsertib and GS-607509 at the intensive PK visit, as appropriate:

Parameter	Description
AUC_{tau}	area under the concentration versus time curve over the dosing interval
C_{last}	last observed quantifiable concentration of the drug in plasma
C_{max}	maximum observed concentration of drug in plasma
C_{tau}	observed drug concentration at the end of the dosing interval
T_{last}	time (observed time point) of C_{last}
T_{max}	time (observed time point) of C_{max}
λ_z	terminal elimination rate constant; estimated by linear regression of the terminal elimination phase of the plasma concentration of drug versus time curve
$t_{1/2}$	estimate of the terminal elimination half-life of the drug in plasma, calculated by dividing the natural log of 2 by the terminal elimination rate constant (λz)
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 (for selonsertib only)

Individual subject concentration data and individual subject PK parameters for selonsertib and its metabolite GS-607509 will be listed and summarized using descriptive statistics for the selonsertib + prednisolone group for subjects participating in the PK substudy. Summary statistics (sample size, mean, SD, coefficient of variation [%CV], median, min, max, Q1, and Q3) will be presented for both individual subject concentration data by time point and individual subject PK parameters. Moreover, the geometric mean, 95% CI, and the mean and SD of the natural log-transformed values will be presented for individual subject PK parameter data.

Individual concentration data listings and summaries will include all subjects with concentration data. The sample size for each time point will be based on the number of subjects with nonmissing concentration data at that time point. The number of subjects with concentration BLQ will be presented for each time point. For summary statistics, BLQ values will be treated as 0 at predose and one-half of the lower limit of quantitation (LLOQ) for postdose time points, where LLOQ is corrected for the dilution factor (ie, reported dilution/dilution factor).

Individual PK parameter data listings and summaries will include all subjects for whom PK parameter(s) can be derived. The sample size for each PK parameter will be based on the number of subjects with nonmissing data for that PK parameter.

The following tables will be provided for each analyte for the Selonsertib+Prednisolone group:

- Individual subject concentration data and summary statistics
- Individual subject plasma PK parameters and summary statistics

The Mean (± SD) concentration data versus time (on linear and semilogarithmic scales) will be provided for each analyte for subjects in the Selonsertib + Prednisolone group. Individual, mean postdose concentration values that are ≤ LLOQ will not be displayed in the figures and remaining points connected.

The following listings will be provided:

- PK sampling details by subject including actual dosing time and actual draw time, calculated time postdose of sample collection, differences in scheduled and actual draw time, sample age and sample concentration.
- Individual data on determination of plasma half-life and corresponding correlation coefficient by analyte

8.3. PK Analyses Related to Sparse PK Sampling

Plasma concentrations of selonsertib and GS-607509 over time will be listed and summarized by nominal visit for subjects in the Selonsertib + Prednisolone group. Single PK concentration data along with the actual collection time and dosing time, and calculated time postdose of sample collection will be included in the PK sampling details listing as described above.

9. REFERENCES

Louvet A, Labreuche J, Artru F, Boursier J, Kim DJ, O'Grady J, et al. Combining Data From Liver Disease Scoring Systems Better Predicts Outcomes of Patients With Alcoholic Hepatitis. Gastroenterology 2015;149 (2):398-406 e8.

Louvet A, Naveau S, Abdelnour M, Ramond MJ, Diaz E, Fartoux L, et al. The Lille model: a new tool for therapeutic strategy in patients with severe alcoholic hepatitis treated with steroids. Hepatology 2007;45 (6):1348-54.

10. SOFTWARE

SAS® Software Version 9.X. SAS Institute Inc., Cary, NC, USA.

nQuery Advisor(R) Version X.0. Statistical Solutions, Cork, Ireland.

11. SAP REVISION

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

12. APPENDICES

Appendix 1. Table of Contents for Statistical Tables, Figures, and Listings

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15.8.2.2	Important Protocol Deviations	Randomized Analysis Set
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15.8.3.1.2	Demographics	Full Analysis Set
15.8.3.2.1	Baseline Characteristics	Safety Analysis Set
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15.8.3.2.3	Daily Alcohol Consumption (g/day), Baseline Height, Weight, and Body Mass Index by Sex	Safety Analysis Set
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15.8.4	Adherence to Study Drug Regimen	Safety Analysis Set
15.9.1.1	Number (%) of Subjects with Death On/Prior to Study Day 28 and Weeks 8, 12, and 24	Subjects with Death/Follow-Up Through Timepoint of Interest (Full Analysis Set)
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15.9.1.3	Kaplan-Meier Estimate of Survival	Full Analysis Set
15.9.1.4	Support for Table 15.9.1.3: Listing of Days and Censoring Status of Survival	Full Analysis Set
15.9.1.5	Kaplan-Meier Estimate of Survival	Modified ITT Analysis Set
15.9.1.6	Support for Table 15.9.1.5: Listing of Days and Censoring Status of Survival	Modified ITT Analysis Set
15.9.1.7	Kaplan-Meier Estimate of Transplantation-Free Survival	Full Analysis Set
15.9.1.8	Support for Table 15.9.1.7: Listing of Days and Censoring Status of Transplantation-Free Survival	Full Analysis Set
15.9.1.9	Kaplan-Meier Estimate of Transplantation-Free Survival	Modified ITT Analysis Set

Table Number	Description	Analysis Set
15.9.1.10	Support for Table 15.9.1.9: Listing of Days and Censoring Status of Transplantation-Free Survival	Modified ITT Analysis Set
15.9.2.1.1	Number (%) of Subjects with Liver Transplant On/Prior to Study Day 28 and Weeks 8, 12, and 24	Subjects with Liver Transplant/Follow-Up Through Timepoint of Interest (Full Analysis Set)
15.9.2.1.2	Number (%) of Subjects with Liver Transplant On/Prior to Study Day 28 and Weeks 8, 12, and 24	Subjects with Liver Transplant/Follow-Up Through Timepoint of Interest (Modified ITT Analysis Set)
15.9.2.2.1	Lille Score by On-Treatment Visit (Covance Central Laboratory Results)	Full Analysis Set
15.9.2.2.2	Lille Score by On-Treatment Visit (Covance Central Laboratory Results)	Modified ITT Analysis Set
15.9.2.2.3	Lille Score at Week 1, Week 2, and Week 4 [LOCF] for Categorical Outcomes (Covance Central Laboratory Results)	Full Analysis Set
15.9.2.2.4	Lille Score at Week 1, Week 2, and Week 4 [LOCF] for Categorical Outcomes (Covance Central Laboratory Results)	Modified ITT Analysis Set
15.9.2.2.5	Mortality Risk at Months 2 and 6 Based on Lille Score at Week 1 and Baseline MELD Score (Covance Central Laboratory Results)	Full Analysis Set
15.9.2.2.6	Mortality Risk at Months 2 and 6 Based on Lille Score at Week 1 and Baseline MELD Score (Covance Central Laboratory Results)	Modified ITT Analysis Set
15.9.2.3.1	Postbaseline Definite Infections Reported Through End of Study (by High Level Group Term and Low Level Term)	Full Analysis Set
15.9.2.3.2	Postbaseline Definite Infections Reported Through End of Study (by High Level Group Term and Low Level Term)	Modified ITT Set
15.9.2.3.3	Postbaseline Definite or Probable Infections Reported Through End of Study (by High Level Group Term and Low Level Term)	Full Analysis Set
15.9.2.3.4	Postbaseline Definite or Probable Infections Reported Through End of Study (by High Level Group Term and Low Level Term)	Modified ITT Analysis Set
15.9.2.3.5	Postbaseline Medications Administered to Treat Infections Through End of Study	Full Analysis Set
15.9.2.3.6	Postbaseline Medications Administered to Treat Infections Through End of Study	Modified ITT Analysis Set
15.9.2.4.1	Postbaseline Hepatorenal Syndrome Events Reported Through End of Study	Full Analysis Set
15.9.2.4.2	Postbaseline Hepatorenal Syndrome Events Reported Through End of Study	Modified ITT Analysis Set
15.9.2.4.3	Postbaseline Medications Administered to Treat Hepatorenal Syndrome Through End of Study	Full Analysis Set

Table Number	Description	Analysis Set
15.9.2.4.4	Postbaseline Medications Administered to Treat Hepatorenal Syndrome Through End of Study	Modified ITT Analysis Set
15.9.2.5.1	Summary of Length of Initial Hospital Stay (Days) from First Dose Date of Study Drug	Full Analysis Set
15.9.2.5.2	Summary of Length of Initial Hospital Stay (Days) from First Dose Date of Study Drug	Modified ITT Analysis Set
15.9.2.6.1	ALT (U/L) and Change and Percentage Change from Baseline by Visit	Full Analysis Set
15.9.2.6.2	ALT (U/L) and Change and Percentage Change from Baseline by Visit	Modified ITT Analysis Set
15.9.2.6.3	AST (U/L) and Change and Percentage Change from Baseline by Visit	Full Analysis Set
15.9.2.6.4	AST (U/L) and Change and Percentage Change from Baseline by Visit	Modified ITT Analysis Set
15.9.2.6.5	GGT (U/L) and Change and Percentage Change from Baseline by Visit	Full Analysis Set
15.9.2.6.6	GGT (U/L) and Change and Percentage Change from Baseline by Visit	Modified ITT Analysis Set
15.9.2.6.7	Albumin (g/dL) and Change and Percentage Change from Baseline by Visit	Full Analysis Set
15.9.2.6.8	Albumin (g/dL) and Change and Percentage Change from Baseline by Visit	Modified ITT Analysis Set
15.9.2.6.9	Alkaline Phosphatase (U/L) and Change and Percentage Change from Baseline by Visit	Full Analysis Set
15.9.2.6.10	Alkaline Phosphatase (U/L) and Change and Percentage Change from Baseline by Visit	Modified ITT Analysis Set
15.9.2.6.11	Total Bilirubin (mg/dL) and Change and Percentage Change from Baseline by Visit	Full Analysis Set
15.9.2.6.12	Total Bilirubin (mg/dL) and Change and Percentage Change from Baseline by Visit	Modified ITT Analysis Set
15.9.2.6.13	Direct Bilirubin (mg/dL) and Change and Percentage Change from Baseline by Visit	Full Analysis Set
15.9.2.6.14	Direct Bilirubin (mg/dL) and Change and Percentage Change from Baseline by Visit	Modified ITT Analysis Set
15.9.2.6.15	INR and Change and Percentage Change from Baseline by Visit	Full Analysis Set
15.9.2.6.16	INR and Change and Percentage Change from Baseline by Visit	Modified ITT Analysis Set
15.9.2.7.1	MELD Score and Change and Percentage Change from Baseline by Visit	Full Analysis Set
15.9.2.7.2	MELD Score and Change and Percentage Change from Baseline by Visit	Modified ITT Analysis Set

Table Number	Description	Analysis Set
15.9.2.7.3	CPT Score and Change and Percentage Change from Baseline by Visit	Full Analysis Set
15.9.2.7.4	CPT Score and Change and Percentage Change from Baseline by Visit	Modified ITT Analysis Set
15.9.2.7.5	Maddrey's DF Score and Change and Percentage Change from Baseline by Visit	Full Analysis Set
15.9.2.7.6	Maddrey's DF Score and Change and Percentage Change from Baseline by Visit	Modified ITT Analysis Set
15.9.3.1.1	ELF Test Score and Change and Percentage Change from Baseline by Visit (Subjects with Nonmissing Baseline and Week 4 Values)	Full Analysis Set
15.9.3.1.2	ELF Test Score and Change and Percentage Change from Baseline by Visit (Subjects with Nonmissing Baseline and Week 4 Values)	Modified ITT Analysis Set
15.9.3.1.3	Hyaluronic Acid and Change and Percentage Change from Baseline by Visit (Subjects with Nonmissing Baseline and Week 4 Values)	Full Analysis Set
15.9.3.1.4	Hyaluronic Acid and Change and Percentage Change from Baseline by Visit (Subjects with Nonmissing Baseline and Week 4 Values)	Modified ITT Analysis Set
15.9.3.1.5	PIIINP and Change and Percentage Change from Baseline by Visit (Subjects with Nonmissing Baseline and Week 4 Values)	Full Analysis Set
15.9.3.1.6	PIIINP and Change and Percentage Change from Baseline by Visit (Subjects with Nonmissing Baseline and Week 4 Values)	Modified ITT Analysis Set
15.9.3.1.7	TIMP-1 and Change and Percentage Change from Baseline by Visit (Subjects with Nonmissing Baseline and Week 4 Values)	Full Analysis Set
15.9.3.1.8	TIMP-1 and Change and Percentage Change from Baseline by Visit (Subjects with Nonmissing Baseline and Week 4 Values)	Modified ITT Analysis Set
15.9.3.2.1	Number (%) of Subjects with Recidivism to Alcohol by Visit	Full Analysis Set
15.9.3.2.2	Number (%) of Subjects with Recidivism to Alcohol by Visit	Modified ITT Analysis Set
15.9.3.3.1	HbA1c and Change and Percentage Change from Baseline	Full Analysis Set
15.9.3.3.2	HbA1c and Change and Percentage Change from Baseline	Modified ITT Analysis Set
15.9.4.1	Number (%) of Subjects with Death On/Prior to Study Day 28 by Subgroup (Subjects with Death/Follow-Up Through Day 28)	Full Analysis Set
15.9.4.2	Number (%) of Subjects with Death On/Prior to Week 8 by Subgroup (Subjects with Death/Follow-Up Through Week 8)	Full Analysis Set
15.9.4.3	Lille Score (Complete, Partial, and Null Response) at Week 1 by Subgroup (Missing Lille Score at Visit = Null Response)	Full Analysis Set
15.9.4.4	Lille Score (Complete, Partial, and Null Response) at Week 2 by Subgroup (Missing Lille Score at Visit = Null Response)	Full Analysis Set
15.9.4.5	Lille Score (Complete, Partial, and Null Response) at Week 4 (LOCF) by Subgroup (Missing Lille Score at Visit = Null Response)	Full Analysis Set

Table Number	Description	Analysis Set
15.10.1.1	Plasma Selonsertib Concentrations (ng/mL) by Subject with Summary Statistics for Each Substudy Timepoint	PK Substudy Analysis Set
15.10.1.2	Plasma GS-607509 Concentrations (ng/mL) by Subject with Summary Statistics for Each Substudy Timepoint	PK Substudy Analysis Set
15.10.1.3	Plasma Selonsertib Pharmacokinetic Parameters by Subject with Summary Statistics for Each Parameter	PK Substudy Analysis Set
15.10.1.4	Plasma GS-607509 Pharmacokinetic Parameters by Subject with Summary Statistics for Each Parameter	PK Substudy Analysis Set
15.10.1.5	Plasma Selonsertib Concentrations (ng/mL) by Subject with Summary Statistics for Each Sparse Sampling Timepoint	PK Analysis Set
15.10.1.6	Plasma GS-607509 Concentrations (ng/mL) by Subject with Summary Statistics for Each Sparse Sampling Timepoint	PK Analysis Set
15.11.1	Extent of Exposure to Study Drug Regimen	Safety Analysis Set
15.11.2.1.1	Treatment-Emergent Adverse Events: Overall Summary	Safety Analysis Set
15.11.2.1.2	Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	Safety Analysis Set
15.11.2.1.3	Treatment-Emergent Adverse Events Occurring in At Least 10% of Subjects Within Any Treatment Group by Preferred Term	Safety Analysis Set
15.11.2.1.4	Treatment-Emergent Adverse Events by System Organ Class, High Level Term, and Preferred Term	Safety Analysis Set
15.11.2.2.1.1	Grade 3 or Higher Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Severity	Safety Analysis Set
15.11.2.2.1.2	Grade 3 or Higher Treatment-Emergent Adverse Events by Preferred Term	Safety Analysis Set
15.11.2.2.2	Grade 2 or Higher Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	Safety Analysis Set
15.11.2.3.1.1	Treatment-Emergent Treatment-Related Adverse Events by System Organ Class and Preferred Term	Safety Analysis Set
15.11.2.3.1.2	Treatment-Emergent Treatment-Related Adverse Events Occurring in at Least 5% of Subjects Within Any Treatment Group by Preferred Term	Safety Analysis Set
15.11.2.3.2.1	Grade 3 or Higher Treatment-Emergent Treatment-Related Adverse Events by System Organ Class, Preferred Term, and Severity	Safety Analysis Set
15.11.2.3.2.2	Grade 3 or Higher Treatment-Emergent Treatment-Related Adverse Events by Preferred Term	Safety Analysis Set
15.11.2.3.3	Grade 2 or Higher Treatment-Emergent Treatment-Related Adverse Events by System Organ Class and Preferred Term	Safety Analysis Set
15.11.2.4.1	Adverse Events Prior to First Dose of Study Drug by System Organ Class and Preferred Term	Safety Analysis Set

Table Number	Description	Analysis Set
15.11.2.4.2	Summary of Subjects Meeting Any Selonsertib/Placebo Stopping Criteria	Safety Analysis Set
15.11.2.4.3	Grade 3 or Higher Treatment-Emergent Treatment-Related Adverse Event Leading to Premature Discontinuation of Selonsertib/Placebo by Preferred Term	Safety Analysis Set
15.11.2.4.4	Selonsertib/Placebo Laboratory Stopping Criteria	Safety Analysis Set
15.11.3	Treatment-Emergent Adverse Events with an Outcome of Death by System Organ Class and Preferred Term	Safety Analysis Set
15.11.4.1	Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term	Safety Analysis Set
15.11.4.2	Treatment-Emergent Serious Adverse Events by Preferred Term	Safety Analysis Set
15.11.4.3	Treatment-Emergent Serious Adverse Events by System Organ Class, High Level Term, and Preferred Term	Safety Analysis Set
15.11.4.4	Treatment-Emergent Treatment-Related Serious Adverse Events by System Organ Class and Preferred Term	Safety Analysis Set
15.11.4.5	Treatment-Emergent Treatment-Related Serious Adverse Events by Preferred Term	Safety Analysis Set
15.11.5.1	Treatment-Emergent Adverse Events Leading to Premature Discontinuation of Selonsertib/Placebo	Safety Analysis Set
15.11.5.2	Treatment-Emergent Adverse Events Leading to Premature Discontinuation of Prednisolone	Safety Analysis Set
15.11.5.3	Treatment-Emergent Adverse Events Leading to Premature Discontinuation of Both Study Drugs in the Regimen	Safety Analysis Set
15.11.5.4	Treatment-Emergent Adverse Events Leading to Interruption of Selonsertib/Placebo	Safety Analysis Set
15.11.5.5	Treatment-Emergent Adverse Events Leading to Interruption of Prednisolone	Safety Analysis Set
15.11.5.6	Treatment-Emergent Adverse Events Leading to Dose Modification or Interruption of Prednisolone	Safety Analysis Set
15.11.6.1.1	Hemoglobin (g/dL) and Change from Baseline	Safety Analysis Set
15.11.6.1.2	Hematocrit (%) and Change from Baseline	Safety Analysis Set
15.11.6.1.3	Lymphocytes (x10^3/µL) and Change from Baseline	Safety Analysis Set
15.11.6.1.4	Neutrophils (x10^3/µL) and Change from Baseline	Safety Analysis Set
15.11.6.1.5	Platelet Count (x10^3/µL) and Change from Baseline	Safety Analysis Set
15.11.6.1.6	White Blood Cells (x10^3/µL) and Change from Baseline	Safety Analysis Set
15.11.6.1.7	Bicarbonate (mEq/L) and Change from Baseline	Safety Analysis Set
15.11.6.1.8	Sodium (mEq/L) and Change from Baseline	Safety Analysis Set
15.11.6.1.9	Chloride (mEq/L) and Change from Baseline	Safety Analysis Set
15.11.6.1.10	Magnesium (mg/dL) and Change from Baseline	Safety Analysis Set

Table Number	Description	Analysis Set
15.11.6.1.11	Phosphorus (mg/dL) and Change from Baseline	Safety Analysis Set
15.11.6.1.12	Potassium (mEq/L) and Change from Baseline	Safety Analysis Set
15.11.6.1.13	Albumin Corrected Calcium (mg/dL) and Change from Baseline	Safety Analysis Set
15.11.6.1.14	Lactate Dehydrogenase (U/L) and Change from Baseline	Safety Analysis Set
15.11.6.1.15	Blood Urea Nitrogen (mg/dL) and Change from Baseline	Safety Analysis Set
15.11.6.1.16	Serum Creatinine (mg/dL) and Change from Baseline	Safety Analysis Set
15.11.6.1.17	Serum Glucose (mg/dL) and Change from Baseline	Safety Analysis Set
15.11.6.2	Treatment-Emergent Grade 3 or 4 Laboratory Abnormalities	Safety Analysis Set
15.11.6.3	Treatment-Emergent Marked Laboratory Abnormalities	Safety Analysis Set
15.11.7.1.1	Systolic Blood Pressure (mmHg) and Change from Baseline	Safety Analysis Set
15.11.7.1.2	Diastolic Blood Pressure (mmHg) and Change from Baseline	Safety Analysis Set
15.11.7.1.3	Pulse (beats/min) and Change from Baseline	Safety Analysis Set
15.11.7.2.1	Concomitant Medications by Preferred Drug Name	Safety Analysis Set
15.11.7.2.2	Concomitant Enteral and Parenteral Nutrition by Preferred Drug Name	Safety Analysis Set
15.11.8.1	Shift Table of Baseline vs. Postbaseline 12-Lead ECG Assessments	Safety Analysis Set

Figure Number	Description	Analysis Set
15.8.1	Disposition of Study Subjects	Safety Analysis Set
15.9.1.1	Kaplan-Meier Estimates of Survival	Full Analysis Set
15.9.1.2	Kaplan-Meier Estimates of Survival	Modified ITT Analysis Set
15.9.1.3	Kaplan-Meier Estimates of Transplantation-Free Survival	Full Analysis Set
15.9.1.4	Kaplan-Meier Estimates of Transplantation-Free Survival	Modified ITT Analysis Set
15.9.2.2.1	Median (Q1, Q3) Lille Score by On-Treatment Visit (Covance Central Laboratory Results)	Full Analysis Set
15.9.2.2.2	Median (Q1, Q3) Lille Score by On-Treatment Visit (Covance Central Laboratory Results)	Modified ITT Analysis Set
15.9.2.2.1	Median (Q1, Q3) MELD Score by Visit	Full Analysis Set
15.9.2.2.2	Median (Q1, Q3) MELD Score by Visit	Modified ITT Analysis Set
15.9.2.2.3	Median (Q1, Q3) Change from Baseline in MELD Score by Visit	Full Analysis Set
15.9.2.2.4	Median (Q1, Q3) Change from Baseline in MELD Score by Visit	Modified ITT Analysis Set
15.9.2.2.5	Median (Q1, Q3) Percentage Change from Baseline in MELD Score by Visit	Full Analysis Set
15.9.2.2.6	Median (Q1, Q3) Percentage Change from Baseline in MELD Score by Visit	Modified ITT Analysis Set
15.9.2.3.1	Median (Q1, Q3) Total Bilirubin (mg/dL) by Visit	Full Analysis Set
15.9.2.3.2	Median (Q1, Q3) Total Bilirubin (mg/dL) by Visit	Modified ITT Analysis Set
15.9.2.3.3	Median (Q1, Q3) Change from Baseline in Total Bilirubin (mg/dL) by Visit	Full Analysis Set
15.9.2.3.4	Median (Q1, Q3) Change from Baseline in Total Bilirubin (mg/dL) by Visit	Modified ITT Analysis Set
15.9.2.3.5	Median (Q1, Q3) Percentage Change from Baseline in Total Bilirubin by Visit	Full Analysis Set
15.9.2.3.6	Median (Q1, Q3) Percentage Change from Baseline in Total Bilirubin by Visit	Modified ITT Analysis Set
15.9.2.4.1	Median (Q1, Q3) ALT (U/L) by Visit	Full Analysis Set
15.9.2.4.2	Median (Q1, Q3) ALT (U/L) by Visit	Modified ITT Analysis Set
15.9.2.5.1	Median (Q1, Q3) AST (U/L) by Visit	Full Analysis Set
15.9.2.5.2	Median (Q1, Q3) AST (U/L) by Visit	Modified ITT Analysis Set
15.9.2.6.1	Median (Q1, Q3) INR by Visit	Full Analysis Set
15.9.2.6.2	Median (Q1, Q3) INR by Visit	Modified ITT Analysis Set

Figure Number	Description	Analysis Set
15.10.1	Mean (SD) Selonsertib Plasma Concentration vs Time (Linear and Semilogarithmic Scale)	PK Substudy Analysis Set
15.10.2	Mean (SD) GS-607509 Plasma Concentration vs Time (Linear and Semilogarithmic Scale)	PK Substudy Analysis Set
15.11.6.1.16	Median (Q1, Q3) Serum Creatinine (mg/dL) by Visit	Safety Analysis Set

Listing Number	Description	Analysis Set
16.1.6	Lot Numbers and Bottle/Carton IDs	Safety Analysis Set
16.1.7	Randomization Scheme and Codes	Randomized Subjects
16.2.1.1	Subject Disposition	Safety Analysis Set
16.2.1.2	Reasons for Screen Failure	Subjects Screened But Not Randomized
16.2.2.1	Important Protocol Deviations	Safety Analysis Set
16.2.2.2	Randomization Stratification Discrepancies between IWRS and Clinical Database	Safety Analysis Set
16.2.2.3	Subjects Who Received Incorrect Study Drug	Safety Analysis Set
16.2.3	Subjects Who Were Excluded From the Safety/mITT and/or Full Analysis Sets	Randomized Subjects
16.2.4.1	Demographics	Safety Analysis Set
16.2.4.2.1	Baseline Characteristics (I)	Safety Analysis Set
16.2.4.2.2	Baseline Characteristics (II)	Safety Analysis Set
16.2.4.2.3	Baseline Characteristics (III)	Safety Analysis Set
16.2.4.2.4	Baseline Characteristics (IV)	Safety Analysis Set
16.2.4.2.5	Baseline Characteristics (V)	Safety Analysis Set
16.2.4.2.6	Prior Corticosteroids Administered for Treatment of Alcoholic Hepatitis	Safety Analysis Set
16.2.4.3.1	Medical History	Safety Analysis Set
16.2.4.3.2	Chest X-Ray	Safety Analysis Set
16.2.4.3.3	Liver Imaging	Safety Analysis Set
16.2.4.3.4	Baseline Infections with Cultures and/or PMNC Counts from Ascitic Fluid	Safety Analysis Set
16.2.4.3.5	Prior Medications Used to Treat Baseline Infections	Safety Analysis Set
16.2.4.4.1	Prior and Concomitant Medications	Safety Analysis Set
16.2.4.4.2	Prior and Concomitant Enteral and Parenteral Nutrition	Safety Analysis Set
16.2.5.1	Study Drug Administration	Safety Analysis Set
16.2.5.2	Subjects Who Prematurely Discontinued Any of the Study Drugs	Safety Analysis Set
16.2.5.3	Study Drug Accountability and Adherence	Safety Analysis Set
16.2.5.4.1	Plasma Pharmacokinetic Sampling Details and Concentrations	PK Analysis Set
16.2.5.4.2	Terminal Elimination Rate Constant and Half Life of Drug	PK Substudy Analysis Set
16.2.6.1.1	Deaths	Modified ITT Analysis Set
16.2.6.1.2	Liver Transplants	Modified ITT Analysis Set
16.2.6.2.1	Lille Scores (Covance Central Laboratory Results)	Modified ITT Analysis Set

Listing Number	Description	Analysis Set
16.2.6.2.2	Categorical Efficacy Endpoints for Lille Score and Death	Modified ITT Analysis Set
16.2.6.3	MELD Score, Total Bilirubin, and Direct Bilirubin and Change and Percentage Change from Baseline (Efficacy Visit Windows Through Week 8)	Modified ITT Analysis Set
16.2.6.4	CPT Score and Maddrey's Discriminant Function and Change and Percentage Change from Baseline (Efficacy Visit Windows Through Week 8)	Modified ITT Analysis Set
16.2.6.5	AST, ALT, and Alkaline Phosphatase and Change and Percentage Change from Baseline (Efficacy Visit Windows Through Week 8)	Modified ITT Analysis Set
16.2.6.6	GGT, Albumin and INR and Change and Percentage Change from Baseline (Efficacy Visit Windows Through Week 8)	Modified ITT Analysis Set
16.2.6.7.1	Postbaseline Definite or Probable Infections Reported Through End of Study	Modified ITT Analysis Set
16.2.6.7.2	Postbaseline Cultures, X-Rays, and/or Polymorphonuclear Cell Counts from Ascitic Fluid for Infections	Modified ITT Analysis Set
16.2.6.7.3	Postbaseline Medications Administered to Treat Infections Through End of Study	Modified ITT Analysis Set
16.2.6.8.1	Postbaseline Hepatorenal Syndrome (HRS)	Modified ITT Analysis Set
16.2.6.8.2	Postbaseline Medications Used to Treat Hepatorenal Syndrome	Modified ITT Analysis Set
16.2.6.9	Length of Initial Hospital Stay (Days) from First Study Drug Dose Date	Modified ITT Analysis Set
16.2.6.10.1	ELF Score and Hyaluronic Acid and Change and Percentage Change from Baseline (Efficacy Visit Windows Through Week 4)	Modified ITT Analysis Set
16.2.6.10.2	PIIINP and TIMP-1 and Change and Percentage Change from Baseline (Efficacy Visit Windows Through Week 4)	Modified ITT Analysis Set
16.2.7.1	Adverse Events	Safety Analysis Set
16.2.7.2	Adverse Events Leading to Death	Safety Analysis Set
16.2.7.3.1	Serious Adverse Events	Safety Analysis Set
16.2.7.3.2	Serious Adverse Events Related to Study Treatment	Safety Analysis Set
16.2.7.4.1	Adverse Events with Severity of Grade 3 or Higher	Safety Analysis Set
16.2.7.4.2	Adverse Events with Severity of Grade 3 or Higher Related to Study Treatment	Safety Analysis Set
16.2.7.5.1	Adverse Events Leading to Premature Discontinuation of Any of the Study Drugs	Safety Analysis Set
16.2.7.5.2	Adverse Events Leading to Dose Modification or Interruption of Any of the Study Drugs	Safety Analysis Set

Listing Number	Description	Analysis Set
16.2.7.6.1	Selonsertib/Placebo Stopping Criteria 1: Grade 3 or Higher AEs Related to Study Drug that Led to Premature Discontinuation of Selonsertib/Placebo	Safety Analysis Set
16.2.7.6.2	Selonsertib/Placebo Stopping Criteria 2: Lille Score > 0.85 While on Study Drug	Safety Analysis Set
16.2.7.6.3	Selonsertib/Placebo Stopping Criteria 3: Death On/Prior to Study Day 28	Safety Analysis Set
16.2.7.6.4.1	Selonsertib/Placebo Stopping Criteria 4.1: Confirmed ALT or AST > 5 X Baseline While on Study Drug	Safety Analysis Set
16.2.7.6.4.2	Selonsertib/Placebo Stopping Criteria 4.2: ALT or AST > 500 U/L While on Study Drug	Safety Analysis Set
16.2.7.6.4.3	Selonsertib/Placebo Stopping Criteria 4.3: Confirmed Total Bilirubin > 3 X Baseline or Nadir While on Study Drug	Safety Analysis Set
16.2.8.1.1.1	Local and Covance Laboratory Screening Tests I	Safety Analysis Set
16.2.8.1.1.2	Local and Covance Laboratory Screening Tests II	Safety Analysis Set
16.2.8.1.1.3	Covance Urine Drug Screen: Amphetamines/MDMA, Cocaine, Opiates, and Cannabinoids	Safety Analysis Set
16.2.8.1.1.4	Central Laboratory (Covance) Reference Ranges	
16.2.8.1.2.1	Hematology: Hematocrit, Hemoglobin, RBC, MCV, MCH, MCHC, and Platelets	Safety Analysis Set
16.2.8.1.2.2	Hematology: WBC, Neutrophils, and Lymphocytes	Safety Analysis Set
16.2.8.1.2.3	Hematology: Eosinophils, Basophils, and Monocytes	Safety Analysis Set
16.2.8.1.3.1	Chemistry: Sodium, Postassium, Bicarbonate, Chloride, Phosphorus, and Magnesium	Safety Analysis Set
16.2.8.1.3.2	Chemistry: Calcium, Calcium Corrected for Albumin, LDH, BUN, Uric Acid, Total Protein, and Serum Creatinine	Safety Analysis Set
16.2.8.1.3.3	Liver Related Chemistry: AST, ALT, Total Bilirubin, Direct Bilirubin, Alkaline Phosphatase, GGT, and Albumin	Safety Analysis Set
16.2.8.1.4	Coagulation: Prothrombin Time, Prothrombin Time Control, INR, and APTT	Safety Analysis Set
16.2.8.1.5.1	Lipids: Triglycerides, Total Cholesterol, HDL, and Calculated LDL and VLDL	Safety Analyis Set
16.2.8.1.5.2	Other: Insulin and HbA1c	Modified ITT Analysis Set
16.2.8.1.5.3	Other: Urine Pregnancy Test Results (Female Subjects)	Safety Analysis Set
16.2.8.1.6	Treatment-Emergent Grade 3 or Higher Laboratory Abnormalities	Safety Analysis Set
16.2.8.2.1	Body Height, Weight, BMI, and Vital Signs	Safety Analysis Set
16.2.8.2.2	12-Lead ECG Assessment	Safety Analysis Set
16.2.8.3	Pregnancy Report	Safety Analysis Set

Appendix 2. GS-US-416-2124 Programming Specifications

Lille Score Imputations

Subjects missing a Covance-calculated Lille score at Week 1 who have a calculable value at Week 1 using local laboratory data (flagged with '*') will have local laboratory data used in place of Covance data for their entire duration of treatment. Subjects missing central laboratory data at Week 1 and the reason for the data being missing is outlined below:

Subject ID	Reason for Missing Data
PPD	Both screening and Day 1 central laboratory samples were drawn, but were cancelled due to samples being out of stability when they arrived at Covance.
PPD	Day 1 Prothrombin time and INR were cancelled. No screening central labs were drawn for this subject. Subject stopped both drugs [local labs] at Week 1 for Lille score stopping criteria.
PPD	Week 1 central laboratory total bilirubin was cancelled for "insufficient quantity" by Covance labs. Biomarker samples were not covered with a light resistant substance (total bilirubin requires covering) so could not be used to retest. Subject stopped prednisolone at Week 1 per local laboratory values.
PPD	Week 1 central laboratory total bilirubin was not collected due to difficulties drawing blood.
PPD	INR and PT were cancelled at both screening and baseline by Covance. Local laboratory values will be used.
PPD	Covance labs were not collected by the site at the Week 1 visit. This subject was a "hard stick" and not enough blood could be drawn to run Covance labs. Local laboratory data will be used.

NO IMPUTATION (Lille Score missing at Week 1); use Covance results for Lille scores:

PPD	Subject was hospitalized at Week 1 for SAE hepatic encephalopathy. Subject enrolled under Amendment 1, so no local laboratory data was collected. Covance laboratory data will be used to calculate MELD score and Week 1 will be missing.
PPD	Week 1 central and local laboratory total bilirubin not collected until Study Day 11 (outside the Week 1 visit window) due to Thanksgiving holiday. Covance laboratory data will be used to calculate MELD score; Week 1 will be missing.
PPD	Protocol Violation reason for early d/c of drug; DIED before Week 1.
PPD	DIED before reaching the Week 1 study visit

Code to be used for Lille scores: Subjects with non-missing values from Covance available to calculate Week 1 Lille score and subjects for whom a Week 1 Lille score is not calculable for both local laboratory and central laboratory data will use Covance laboratory results to calculate Lille scores for all on-treatment visits.

MELD Score Imputations

Subjects missing a baseline Covance MELD score will have their local laboratory screening MELD score (collected to assess inclusion/exclusion criteria and for stratification) used in place of the Covance baseline MELD score (subjects with '#' below). Subjects missing baseline MELD scores from central laboratory data and the reason for their data being missing are outlined below:

Subject ID	Reason for Missing Data
PPD	Serum enzymatic creatinine was not able to be resulted, and sample was not available for retesting using LCMSMS methodology (Covance test kit was Amendment 1 protocol test kit). The subject died in first week and has no postbaseline data. Use local lab screening MELD score.
PPD	Both screening and Day 1 central laboratory samples were drawn, but were cancelled due to samples being out of stability when they arrived at Covance. Use local lab screening MELD score.
PPD	Day 1 Prothrombin time and INR were cancelled by Covance. No screening central labs were drawn for this subject. Use local lab screening MELD score.
PPD	INR and PT were cancelled by Covance at both the screening and baseline visits. Use local lab screening MELD score.