STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety, Tolerability, and Efficacy of GS-9674 in Subjects with Primary Sclerosing Cholangitis Without Cirrhosis
Name of Test Drug:	GS-9674
Study Number:	GS-US-428-4025
Protocol Version (Date):	Protocol Amendment 3, 09 February 2017
Analysis Type:	Primary Analysis and Final Analysis
Analysis Plan Version:	Version 1.1
Analysis Plan Date:	21 March 2018
Analysis Plan Author(s):	PPD

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LIST OF ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
ALP	alkaline phosphatase
ASCVD	atherosclerotic cardiovascular disease
AST	aspartate aminotransferase
BD Phase	blinded study phase
BLQ	below the limit of quantitation
BMI	body mass index
C4	7-alpha-hydroxy-4-cholesten-3-one
CFR	Code of Federal Regulations
CI	confidence interval
CRF	case report form
CSR	clinical study report
CTCAE	common toxicity criteria for adverse events
DILI	drug-induced liver injury
DMC	data monitoring committee
ELF	enhanced liver fibrosis
ECG	electrocardiogram
ET	early termination
FAS	Full Analysis Set
FGF19	fibroblast growth factor 19
FU	follow-up
GGT	gamma glutamyl transferase
GSI	Gilead Sciences, Inc.
HA	hyaluronic acid
HbA1c	hemoglobin A1c
HDL-C	high density lipoprotein-cholesterol
HLT	high-level term
HOMA-IR	homeostatic assessment of insulin resistance
hsCRP	high-sensitivity C-reactive protein
IBD	inflammatory bowel disease
ICH	international conference on harmonization (of technical requirements for registration of pharmaceuticals for human use)
ID	identification
INR	international normalized ratio
IXRS	interactive voice or web response system
LDL-C	low density lipoprotein-cholesterol
LT	long-term
LTT	lower-level term

LOQ	limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
MRE	magnetic resonance elastography
MRCP	magnetic resonance cholangiopancreatography
Non-HDL-C	non high density lipoprotein-cholesterol
OLE	Open Label Extension
PBC	primary biliary cholangitis
PD	pharmacodynamics
PI	principal investigator
PIIINP	procollagen III amino terminal peptide
PK	pharmacokinetics
PP	per protocol
PRO	patient-reported outcome
PSC	primary sclerosing cholangitis
PT	preferred term
PTM	Placebo to match
Q1, Q3	first quartile, third quartile
QoL	quality of life
SAP	statistical analysis plan
SD	standard deviation
SI (units)	international system of units
SOC	system organ class
TE	treatment-emergent
TEAE	treatment-emergent adverse event
TFLs	tables, figures, and listings
TIMP-1	tissue inhibitor of metalloproteinase 1
UDCA	ursodeoxycholic acid
ULN	upper limit of normal
VAS	visual analog scale
VLDL-C	very low density lipoprotein-cholesterol
WHO	World Health Organization

PHARMACOKINETIC ABBREVIATIONS

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

1. INTRODUCTION

This statistical analysis plan (SAP) describes the statistical analysis methods and data presentations to be used in tables, figures, and listings (TFLs) in the clinical study report (CSR) for Study GS-US-428-4025.

This study consists of two phases, a Blinded Study (BD) Phase followed by an Open Label Extension (OLE) Phase. The primary analysis will be performed when all subjects have completed the blinded study treatment and the BD follow-up visit or prematurely discontinued from the study in the BD Phase. The final analysis will be performed when all the subjects have completed the study or prematurely discontinued from the study.

This SAP is based on the study protocol amendment 3 dated 09 February 2017 and the electronic case report form (eCRF). The SAP will be finalized prior to data unblinding for the primary analysis. Any changes made after the finalization of the SAP will be documented in the CSR.

1.1. Study Objectives

The primary objective of this study is as follows:

- To evaluate the safety and tolerability of GS-9674 in subjects with primary sclerosing cholangitis (PSC)

The exploratory objectives of this study are as follows:

1.2. Study Design

This is a Phase 2 randomized, double-blind, placebo-controlled study evaluating the safety, tolerability, and efficacy of GS-9674 in subjects with PSC without cirrhosis.

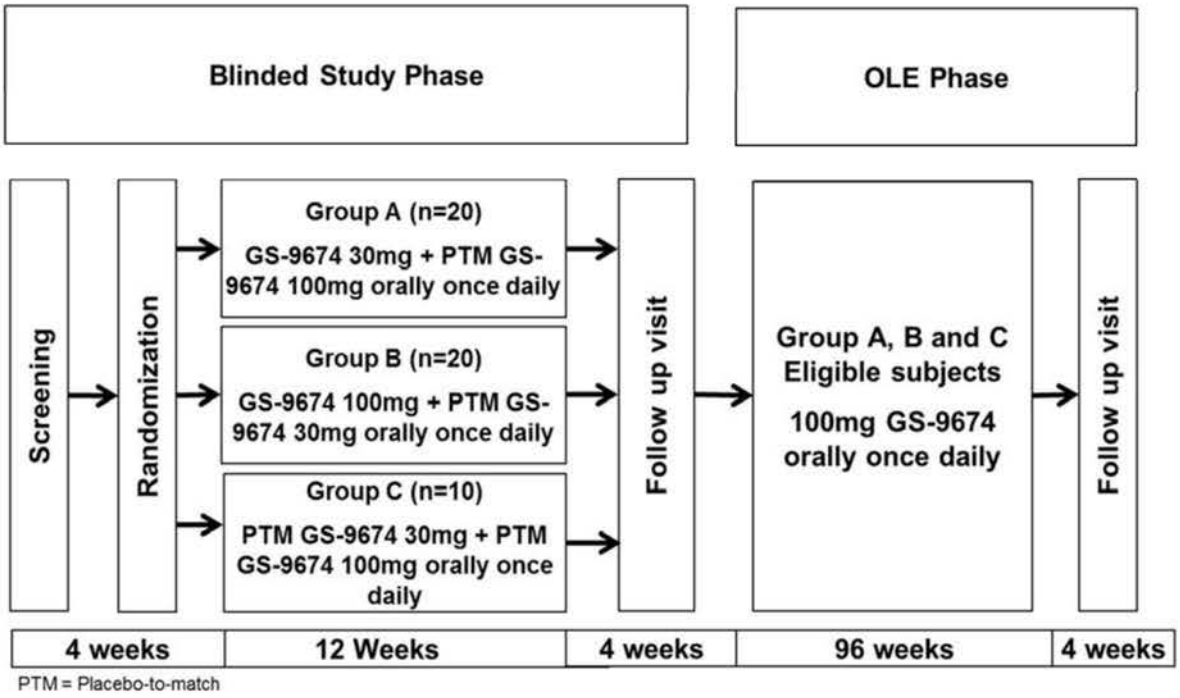
The study consists of 2 phases, a BD Phase and an OLE Phase.

BD Phase: Includes a 4-week screening period, 12 weeks of blinded treatment, and a BD Phase follow-up visit 4 weeks after completion of blinded treatment.

Subjects completing the Blinded Study Phase without permanently discontinuing study drug will be eligible to participate in the OLE Phase of the study.OLE Phase: Includes a 96-week OLE treatment and an OLE Phase follow-up visit 4 weeks after completion of open label treatment.

The overall study design is presented graphically in Figure 1-1.

Figure 1-1. Overall Study Design



Eligible subjects are randomly assigned to 1 of the following 3 treatment groups in a 2:2:1 ratio:

- GS-9674 30 mg + PTM GS-9674 100 mg orally once daily (n = 20);
- GS-9674 100 mg + PTM GS-9674 30 mg orally once daily (n = 20);
- PTM GS-9674 30 mg + PTM GS-9674 100 mg orally once daily (n = 10).

where PTM stands for Placebo to Match.

Central randomization is used. The randomization schedule is stratified by the presence or absence of ursodeoxycholic acid (UDCA) use.

Study drugs are administered for a total of 12 weeks from the Baseline/Day 1 visit during the BD Phase and 96 weeks during the OLE Phase. During the OLE Phase, subjects begin with open label treatment of GS-9674 (100 mg once daily). The dose of GS-9674 may be reduced from 100 mg to 30 mg (or subsequently increased back to 100 mg) at the principal investigator's (PI) discretion with the approval of the medical monitor, as required.

Subjects will be unblinded to their BD Phase treatment assignment after the primary analysis has been completed, approximately 6 weeks after all subjects have completed the BD Phase or early terminated. The schedule of assessments is provided as an appendix to this analysis plan (Appendix 1).

1.3. Sample Size and Power

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

2. TYPE OF PLANNED ANALYSIS

2.1. DMC Interim Analyses

An external multidisciplinary Data Monitoring Committee (DMC) will review the progress of the study and perform interim reviews of the safety data in order to protect subject welfare and preserve study integrity. To ensure the best interests of the participants, the DMC will recommend to the sponsor if the nature, frequency, and severity of adverse effects associated with the study treatment warrant the early termination (ET) of the study, the continuation of the study, or the continuation of the study with modifications.

The initial review will be conducted after first 20 subjects have been randomized. Additional meetings will be scheduled approximately every 3 to 4 months in BD Phase and every 6 months in OLE Phase.

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

While the DMC will be asked to advise Gilead regarding future conduct of the study, including possible early study termination due to a negative safety signal, Gilead retains final decision-making authority on all aspects of the study.

2.2. Primary Analysis

After all subjects have completed the blinded study treatment and the follow-up visit for the BD Phase or discontinued from the study in the BD Phase, outstanding data queries have been resolved or adjudicated as unresolvable, and the data have been cleaned and finalized, the study blind will be broken and the primary analysis of the data will be performed.

2.3. Internal Administrative Review

An administrative interim review of the data will be performed by a Gilead internal unblinded team after all subjects completed 12 weeks of treatment. The purpose of this review was to assess the efficacy and safety of GS-9674 in subjects with PSC without cirrhosis to support further planning and development of this indication. The unblinded team will be independent of the GS-US-428-4025 study team and will not be directly involved in study conduct. Individuals who will be unblinded will be documented on the unblinding form, and the rationale for performing the internal interim review will be documented per Gilead standard operating procedures. The Study Team will remain blinded to treatment assignments until the database is finalized and unblinded for the primary analysis.

2.4. Final Analysis

After all subjects have completed the open label treatment and the follow-up visit for the OLE Phase, or discontinued from study, and data have been cleaned and finalized, the final analysis 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.

This study is not designed to formally test statistical hypotheses. PPD

By-subject listings will be presented for all subjects in the corresponding analysis sets in accordance with tables, and sorted by subject identification (ID) number, visit date, and time (if applicable). Data collected on log forms, such as AEs, will be presented in chronological order within subject. Age, sex at birth, race, and ethnicity will be included in the listings, as space permits.

3.1. Analysis Sets

Analysis sets define the subjects to be included in an analysis. Analysis sets and their definitions are provided in this section. Subjects included in each analysis set in BD Phase will be determined before the study blind is broken for analysis. The analysis set will be identified and included as a subtitle of each table, figure, and listing.

For each analysis set, the number and percentage of subjects eligible for inclusion, as well as the number and percentage of subjects who were excluded and the reasons for their exclusion, will be summarized. The denominator for percentage calculation will be the total number of subjects in the All Randomized Analysis Set by treatment group.

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

3.1.1. All Randomized Analysis Set

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

3.1.2. Full Analysis Set

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

3.1.3. Safety Analysis Set

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

3.1.4. OLE Analysis Set

The OLE Analysis Set includes all subjects who took at least 1 dose of study drug in the OLE Phase. This is the primary analysis set for safety and efficacy analyses during the OLE Phase.

3.1.5. Pharmacokinetic Analysis Set

The Pharmacokinetic (PK) Analysis Set will include all randomized subjects who took at least 1 dose of study drug and have at least 1 nonmissing postdose concentration data of GS-9674 (and its metabolites as applicable) reported by the PK laboratory. This is the primary analysis set for all PK analyses.

3.1.6. Pharmacokinetic Substudy Analysis Set

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3.2. Subject Grouping

For analyses based on the FAS, subjects will be grouped according to the treatment to which they were randomized. For analyses based on the Safety Analysis Set and PK Analysis Set, subjects will be grouped according to actual treatment received. The actual treatment received will differ from the randomized treatment only when their actual treatment differs from randomized treatment for the entire treatment duration in the BD Phase.

For analyses in the BD Phase, subjects will be grouped into the following groups, and only the BD Phase data will be summarized:

1) BD Phase GS-9674 100 mg: This group includes all subjects who were on GS-9674 100 mg in the BD Phase;

2) BD Phase GS-9674 30 mg: This group includes all subjects who were on GS-9674 30 mg in the BD Phase;

3) BD Phase GS-9674 Pooled: This group includes all subjects who were on GS-9674 100 mg or GS-9674 30 mg in the BD Phase;

4) BD Phase Placebo: This group includes all subjects who were on Placebo in the BD Phase.

Treatment groups 1, 2, and 4 will be presented in efficacy tables in BD Phase. Treatment groups 1 - 4 will be presented in all tables other than efficacy tables in BD Phase.

For analyses in the OLE Phase, subjects will be grouped into the following groups, and only the OLE Phase data will be summarized:

5) OLE Phase GS-9674 - Previously in 100 mg: This group includes all subjects who received the OLE study drug and previously received GS-9674 100 mg in the BD Phase;

6) OLE Phase GS-9674 - Previously in 30 mg: This group includes all subjects who received the OLE study drug and previously received GS-9674 30 mg in the BD Phase;

7) OLE Phase GS-9674 - Previously in Placebo: This group includes all subjects who received the OLE study drug and previously received placebo in the BD Phase;

8) OLE Phase GS-9674 Total: This group includes all subjects who received the OLE study drug.

For long-term (LT) analyses, subjects will be grouped into the following groups, and data from both BD Phase and OLE Phase will be summarized:

9) LT GS-9674 initially in 100 mg: This group includes all subjects who received GS-9674 100 mg in the BD Phase and may or may not enter the OLE Phase;

10) LT GS-9674 initially in 30 mg: This group includes all subjects who received GS-9674 30 mg in the BD Phase and may or may not enter the OLE Phase.

3.3. Strata and Covariates

Subjects will be randomly assigned to treatment groups via the interactive voice or web response system (IXRS) in a 2:2:1 ratio using a stratified randomization schedule. Randomization will be stratified by the presence or absence of UDCA use as below:

- Presence of UDCA use at baseline in BD Phase

or

- Absence of UDCA use at baseline in BD Phase

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

3.4. Examination of Subject Subgroups

Subgrouping of subjects based on randomization stratification factors will be explored for subgroup analyses. The subgroups are as follows:

- Subjects with UDCA use at baseline in BD Phase
- Subjects without UDCA use at baseline in BD Phase

See Section 6.4 for details.

3.5. Multiple Comparisons

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

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

3.6.2. Outliers

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

3.7. Data Handling Conventions and Transformations

In general, age (in years) on the date of the first dose of study drug will be used for analyses and presentation in listings. If an enrolled subject was not dosed with any study drug, the randomization date will be used instead of the first dosing date of study drug. For screen failures, the date the informed consent was signed will be used for age calculation. If only the birth year is collected on the case report form (CRF), "01 July" will be used for the unknown birth day and month for the purpose of age calculation. If only birth year and month are collected, "01" will be used for the unknown birth day.

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

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

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

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

3.8. Analysis Visit Windows

3.8.1. Definition of Study Day

Study day/OLE study day will be calculated from the first dosing date of study drug in the BD Phase/OLE Phase and derived as follows:

- For postdose study days: Assessment Date – First Dosing Date of the study phase + 1
- For days prior to the first dose: Assessment Date – First Dosing Date of the study phase

Therefore, BD study Day 1/ OLE study Day 1 is the day of first dose of study drug administration in the corresponding phase.

3.8.2. Analysis Visit Windows

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

The analysis windows to be applied to the BD Phase are provided in Table 3-1, Table 3-2, Table 3-3 and Table 3-4, except that the algorithm for assigning baseline analysis window does not apply to the liver tests (ALP, ALT, AST, and total bilirubin). For these 4 parameters, the baseline values will be determined by averaging the values obtained at screening and Baseline/Day 1, and no specific study day is associated with the average values.

Table 3-1. Analysis Visit Windows in BD Phase for Partial Mayo Score, Vital Signs, Body Weight, Pruritus Measures, Chemistry, Hematology, Coagulation Laboratory, and Mayo Risk Score

Analysis Visit	Study Day	Lower Limit	Upper Limit
Baseline	1	NA	1
Week 1	8	2	11
Week 2	15	12	21
Week 4	29	22	42
Week 8	57	43	70
Week 12	85	71	≥ 85

NA = not applicable

Table 3-2. Analysis Visit Windows in BD Phase for Lipid Profiles and Pooled Cohort Risk Score

Analysis Visit	Study Day	Lower Limit	Upper Limit
Baseline	1	NA	1
Week 1	8	2	18
Week 4	29	19	42
Week 8	57	43	70
Week 12	85	71	≥ 85

NA = not applicable

Table 3-3. Analysis Visit Windows in BD Phase for Fibroscan®, QoL Questionnaires, and Electrocardiogram (ECG), HOMA-IR, HbA1c, C-peptide, Insulin, ELF™ Score, FibroSURE/FibroTest, High-sensitivity C-reactive Protein (hsCRP)

Analysis Visit	Study Day	Lower Limit	Upper Limit
Baseline	1	NA	1
Week 12	85	2	≥ 85

NA = not applicable

Table 3-4. Analysis Visit Windows in BD Phase for FGF19, C4 and Total Bile Acids

Analysis Visit	Study Day	Lower Limit	Upper Limit
Baseline	1	NA	1
Week 1	8	2	18
Week 4	29	19	56
Week 12	85	57	≥ 85

NA = not applicable

The analysis windows to be applied to the OLE Phases are provided in Table 3-5, Table 3-6, Table 3-7, Table 3-8, Table 3-9 and Table 3-10.

Table 3-5. Analysis Visit Windows in OLE Phase for Partial Mayo Score, Vital Signs, Body Weight, Lipid Profiles, Pruritus Measures, Chemistry, Hematology, Coagulation Laboratory, Pooled Cohort Risk Score and Mayo Risk Score

Analysis Visit	OLE Study Day	Lower Limit	Upper Limit
OLE Baseline	1	NA	1
OLE Week 1	8	2	11
OLE Week 2	15	12	21
OLE Week 4	29	22	42
OLE Week 8	57	43	70
OLE Week 12	85	71	126
OLE Week 24	169	127	210
OLE Week 36	253	211	294
OLE Week 48	337	295	378
OLE Week 60	421	379	462
OLE Week 72	505	463	546
OLE Week 84	589	547	630
OLE Week 96	673	631	≥ 673

NA = not applicable

Table 3-6. Analysis Visit Windows in OLE Phase for QoL Questionnaires

Analysis Visit	Study Day	Lower Limit	Upper Limit
OLE Baseline	1	NA	1
OLE Week 4	29	2	56
OLE Week 12	85	57	126
OLE Week 24	169	127	210
OLE Week 36	253	211	294
OLE Week 48	337	295	378
OLE Week 60	421	379	462
OLE Week 72	505	463	546
OLE Week 84	589	547	630
OLE Week 96	673	631	≥ 673

NA = not applicable

Table 3-7. Analysis Visit Windows in OLE Phase ELF™ Score and hsCRP

Analysis Visit	OLE Study Day	Lower Limit	Upper Limit
OLE Baseline	1	NA	1
OLE Week 24	169	2	252
OLE Week 48	337	253	420
OLE Week 72	505	421	588
OLE Week 96	673	589	≥ 673

NA = not applicable

Table 3-8. Analysis Visit Windows in OLE Phase for FGF19, C4, and Total Bile Acids

Analysis Visit	Study Day	Lower Limit	Upper Limit
OLE Baseline	1	NA	1
OLE Week 4	29	2	56
OLE Week 12	85	57	126
OLE Week 24	169	127	252
OLE Week 48	337	253	420
OLE Week 72	505	421	588
OLE Week 96	673	589	≥ 673

NA = not applicable

Table 3-9. Analysis Visit Windows in OLE Phase FibroSURE/FibroTest®

Analysis Visit	OLE Study Day	Lower Limit	Upper Limit
OLE Baseline	1	NA	1
OLE Week 48	337	2	420
OLE Week 72	505	421	588
OLE Week 96	673	589	≥ 673

NA = not applicable

Table 3-10. Analysis Visit Windows in OLE Phase for MRE

Analysis Visit	OLE Study Day	Lower Limit	Upper Limit
OLE Baseline	1	NA	1
OLE Week 48	337	2	505
OLE Week 96	673	506	≥ 673

NA = not applicable
Note: MRE were collected at baseline in BD Phase, OLE Week 48, and Week 96 in OLE Phase, and will not be analyzed until after the completion of the OLE phase. In the analysis, MRE collected at BD Phase baseline will be mapped to the analysis visit "OLE Baseline".

For the safety and efficacy endpoints listed above where visit windows are to be assigned by study phase, data collected up to and including the last dosing date + 30 days of the corresponding phase (and before the first dose of OLE phase for Week 12 visit in BD Phase), will be mapped according to the specified analysis windows unless the nominal visit is ET or follow-up (FU) in BD/OLE phase. For derived risk scores, not all windowed visits are to be summarized or listed in the tables, figures and listings. Refer to Section 6.1.1, 6.2.1, and 6.3.1 for the analysis visits to be presented.

In LT analysis, the above endpoints (except for Pooled Cohort Risk Score and Mayo Risk Score) will first be mapped to visit windows in the BD Phase and the OLE Phase (if applicable), respectively. The LT analysis window will be mapped from their BD Phase window and OLE Phase window:

- The baseline visit of BD Phase is to be mapped to LT Baseline
- The on-treatment visits of BD Phase are to be mapped to the same Week number in LT analysis, ie, Week 1, 2, 4, 8, 12 will be mapped to LT Week 1, 2, 4, 8, 12 accordingly
- The baseline visit of OLE Phase is to be mapped to LT OLE Baseline
- For visits in OLE phase, the on-treatment analysis visits will be mapped to 12 weeks after their originally assigned OLE week numbers, eg, data from OLE Week 1, 2, 4 will be mapped as LT Week 13, 14, 16 accordingly.

The mapping algorithm is provided in Table 3-11.

Table 3-11. Mapping Algorithm from Visit Windows from BD/OLE Phase to LT Analysis

BD/OLE Analysis Visit	LT Analysis Visit	Study Day
Baseline	LT Baseline	1
Week 1	LT Week 1	8
Week 2	LT Week 2	15
Week 4	LT Week 4	29
Week 8	LT Week 8	57
Week 12	LT Week 12	85
OLE Baseline	LT OLE Baseline	85
(OLE Week 1)	(LT Week 13)	92
(OLE Week 2)	(LT Week 14)	99
OLE Week 4	LT Week 16	113
OLE Week 8	LT Week 20	141
OLE Week 12	LT Week 24	169
OLE Week 24	LT Week 36	253
OLE Week 36	LT Week 48	337
OLE Week 48	LT Week 60	421
OLE Week 60	LT Week 72	505
OLE Week 72	LT Week 84	589
OLE Week 84	LT Week 96	673
OLE Week 96	LT Week 108	757

Note: Only map applicable visits per endpoint. LT OLE Baseline visit is not an on-treatment visit, which is included in the LT summary for reference, and carried the target study day as LT Week 12. Summary statistics from LT Week 13 and 14 will not be included in the tables and figures of LT analysis.

Data relating to unscheduled visits may be assigned to a particular visit or time point. The following conventions will be followed:

- An unscheduled visit prior to the first dosing of study drug may be included in the calculation of the baseline value, if applicable.
- Unscheduled visits after the first dose of study drug will be included in determining the maximum postbaseline toxicity grade.
- For subjects who prematurely discontinue from the study, ET data will be summarized as a separate visit, labeled as “Early Termination Visit” of each phase.
- Data collected on a follow-up visit will be summarized as a separate visit and labeled “Follow-up Visit” of each phase.

- In LT analysis, the ET and FU visits from BD/OLE Phase will be considered as "LTET" and "LTFU" visits. However, the LTET and LTFU visits will not be summarized in LT summary tables or figures.

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 in the corresponding study phase, 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. If these multiple measurements occur at the same time or the time is not available, the average of these measurements (for continuous data) will be considered the baseline value.
- Baseline values of the liver tests (ALP, ALT, AST, and total bilirubin) in the BD Phase will be determined by averaging the values obtained at Screening and Baseline/Day 1. For the calculated baseline values, the reference range for each parameter will be defined as the one associated with the latest visit among all the values being averaged for each subject, for the purpose of determination of the abnormality and/or toxicity grades.
- For postbaseline values:
  - The record closest to the nominal day for that visit will be selected.
  - If there are 2 records that are equidistant from the nominal day, the later record will be selected.
  - If there is more than 1 record on the selected day, the average will be taken, unless otherwise specified.

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

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

4. SUBJECT DISPOSITION

4.1. Subject Enrollment and Disposition

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

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

The randomization schedule used for the study will be provided as an appendix to the CSR.

A summary of subject disposition will be provided by treatment group and study phase. This summary will present the number of subjects screened, the number of subjects randomized, and the number of subjects in each of the categories listed below:

- Safety Analysis Set;
- Completed study drug in the BD Phase;
- Did not complete study drug with reasons for premature discontinuation of study drug in BD Phase,
- OLE Analysis Set
- Continuing study drug in the OLE Phase (remove for final analysis);
- Completed study drug in the OLE Phase;
- Did not complete study drug with reasons for premature discontinuation of study drug in the OLE Phase.
- Continuing study (remove for final analysis);
- Completed study;
- Did not complete the study with reasons for premature discontinuation of study.

For the status of study drug and study completion and reasons for premature discontinuation, the number and percentage of subjects in each category will be provided. The denominator for the percentage calculation will be the total number of subjects in the Safety Analysis Set/OLE Analysis Set corresponding to that column in that study phase. In addition, a flowchart will be provided to depict the disposition.

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

- Reasons for premature study drug discontinuation in each study phase or study discontinuation
- Reasons for screen failure will be provided by screening ID number in ascending order
- Lot number and kit ID

4.2. Extent of Study Drug Exposure and Adherence

Extent of exposure to study drug will be examined by assessing the total duration of exposure to study drug and the level of adherence to the study drug specified in the protocol.

4.2.1. Duration of Exposure to Study Drug

For each study phase, total duration of exposure to study drug will be defined as last dose date minus first dose date plus 1 of the reporting phase, regardless of any temporary interruptions in study drug administration, and will be expressed in weeks using up to 1 decimal place (eg, 4.5 weeks). When summarizing cumulative exposure in LT analysis, the sum of exposure in the BD Phase and OLE Phase is used. If the last study drug dose date is missing, the latest date among the study drug end date, clinical visit date, laboratory sample collection date, and vital signs assessment date that occurred during the on-treatment period will be used.

The total duration of exposure to study drug will be summarized using descriptive statistics and using the number (ie, cumulative counts) and percentage of subjects exposed through the following time periods: 1 day, 4 weeks, 8 weeks, and 12 weeks in the BD Phase; 1 day, 4 weeks, 12 weeks, 24 weeks, and every 12 weeks thereafter in the OLE Phase. Summaries will be provided by treatment groups 1 – 4 for the Safety Analysis Set in the BD Phase, 5 – 8 for the OLE Analysis Set in the OLE Phase, and 9 – 10 for the LT analysis, as defined in Section 3.1 and Section 3.2.

No formal statistical testing is planned.

4.2.2. Adherence to Study Drug

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

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

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

4.2.2.1. Adherence in the BD Phase

Prescribed adherence rate will be calculated for the BD Phase and will be provided by treatment groups 1, 2, and 4 by type of tablet for the Safety Analysis Set in the BD Phase. The level of prescribed adherence to the study drug regimen will be determined by the total amount of study drug administered relative to the total amount of study drug specified by the protocol for a subject who completes treatment in the BD Phase.

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

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

Total amount of study drug specified by protocol for the BD Phase is 84 for each type of tablet. Descriptive statistics for the level of prescribed adherence with the number and percentage of subjects belonging to adherence categories (< 75%, ≥ 75 to < 90%, ≥ 90%) will be provided.

4.2.2.2. Adherence in the OLE Phase

On-treatment adherence rate will be calculated for the OLE Phase and will be provided by treatment groups 5 − 8 for the OLE Analysis Set in the OLE Phase. The level of on-treatment adherence to the study drug regimen will be determined by the total amount of study drug administered relative to the total amount of study drug expected to be administered during a subject's actual on-treatment period.

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

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

On-Treatment adherence will be calculated based on overall tablets administered, regardless of the type of the tablets in OLE Phase. Descriptive statistics for the level of on-treatment adherence with the number and percentage of subjects belonging to adherence categories ($< 75\%$, ≥ 75 to $< 90\%$, $\geq 90\%$) will be provided.

No formal statistical testing is planned.

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

4.3. Protocol Deviations

Subjects who did not meet the eligibility criteria for study entry, but enrolled in the study will be summarized regardless of whether they were exempted by the sponsor or not. The summary will present the number and percentage of subjects who did not meet at least 1 eligibility criterion and the number and percentage of subjects who did not meet specific criteria by treatment group based on the All Randomized Analysis Set. A by-subject listing will be provided for those subjects who did not meet at least 1 eligibility (inclusion or exclusion) criterion. The listing will present the eligibility criterion (or criteria if more than 1 deviation) that subjects did not meet and related comments, if collected.

Protocol deviations occurring after subjects entered the study are documented during routine monitoring. The number and percentage of subjects with important protocol deviations by deviation reason (eg, nonadherence to study drug, violation of select inclusion/exclusion criteria) will be summarized by treatment group for the All Randomized Analysis Set/OLE Analysis Set per study phase. A by-subject listing will be provided for those subjects with any important protocol deviation.

5. BASELINE CHARACTERISTICS

5.1. Demographics

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

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

5.2. Baseline Characteristics

Other baseline characteristics include:

- Body weight
- Height
- Body mass index (BMI) as a continuous variable and by categories (< 18.5 kg/m^2, 18.5 to < 25 kg/m^2, 25 to < 30 kg/m^2 and ≥ 30 kg/m^2)
- UDCA use (Yes or No, based on concomitant medication page)
- ALP as a continuous variable
- Total bilirubin as a continuous variable and by categories ($\leq$ ULN or $>$ ULN)
- Direct bilirubin
- ALT as a continuous variable and by categories ($<$ ULN and $\geq$ ULN)
- AST as a continuous variable and by categories ($<$ ULN and $\geq$ ULN)
- GGT
- Fasting serum glucose
- Fasting insulin
- Homeostatic assessment of insulin resistance (HOMA-IR)
- Hemoglobin A1c (HbA1c)
- Fasting triglycerides

- Total cholesterol
- High density lipoprotein-cholesterol (HDL-C)
- Calculated fasting low density lipoprotein-cholesterol (LDL-C)
- Calculated fasting very low density lipoprotein-cholesterol (VLDL-C)
- Calculated fasting non high density lipoprotein-cholesterol (Non-HDL-C)
- ELF™ score and components (hyaluronic acid [HA], procollagen III amino terminal peptide [PIIINP], tissue inhibitor of metalloproteinase 1 [TIMP-1])
- FibroSURE/FibroTest® and selected components (α_2-macroglobulin, haptoglobin, apolipoprotein A1)
- FibroScan®
- hsCRP
- Fasting total bile acids
- Albumin
- INR
- Platelets
- Creatinine
- Smoking status at baseline
- Diabetes mellitus diagnosis at baseline (yes or no, based on medical history page)
- Taking hypertension treatment at baseline (yes or no, based on prior and concomitant medication page)
- Inflammatory bowel disease (IBD) history (yes or no, based on medical history page)
- Baseline partial Mayo score for patients with IBD history
- Baseline classification of biliary tree disease due to PSC based on MRCP

These baseline characteristics will be summarized by treatment groups 1 − 4 and overall (Section 3.2) using descriptive statistics for continuous variables and using number and percentage of subjects for categorical variables. The summary of baseline characteristics will be provided for the Safety Analysis Set. In addition, baseline characteristics will be summarized by baseline UDCA use in a separate table. No formal statistical testing is planned.

The tables will be repeated for the OLE Phase by treatment groups 5 − 8 in Section 3.2, except for height, fasting insulin, HOMA-IR, HbA1c, FibroScan, smoking status, diabetes diagnosis, IBD history and baseline classification of biliary tree disease due to PSC based on MRCP, which are not collected in the OLE Phase.

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

5.3. Medical History

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

6. EFFICACY ANALYSES

Efficacy data will be summarized and analyzed based on the FAS for the BD Phase using treatment groups 1, 2, 4. Data from the OLE Phase will be summarized based on the OLE Analysis Set using treatment groups 5 – 8. For the LT analysis, data will be summarized using treatment groups 9 – 10. Refer to Section 3.2 for the detailed grouping of subjects.

6.1. Exploratory Efficacy Endpoints in the BD Phase

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6.2. Exploratory Efficacy Endpoints in OLE Phase

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6.3. Exploratory Efficacy Endpoints in Long Term Analysis

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6.4. Subgroup Analysis of the Exploratory Efficacy Endpoints

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PPD

6.5. Change From Protocol-Specified Efficacy Analyses

PPD

7. SAFETY ANALYSES

Safety data will be summarized based on the Safety Analysis Set for the BD Phase using treatment groups 1 − 4 in Section 3.2, and the LT analysis using treatment groups 9 − 10. Data from OLE Phase will be summarized based on the OLE Analysis Set using treatment groups 5 − 8. Refer to Section 3.2 for the detailed grouping of subjects.

7.1. Adverse Events and Deaths

7.1.1. Adverse Event Dictionary

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

7.1.2. Adverse Event Severity

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

7.1.3. Relationship of Adverse Events to Study Drug

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

7.1.4. Serious Adverse Events

Serious adverse events (SAEs) will be identified and captured as SAEs if the AEs met the definitions of SAEs that were specified in the study protocol. SAEs captured and stored in the clinical database will be reconciled with the SAE database from the Gilead Drug Safety and Public Health 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 in the BD Phase (and before the first dosing date in the OLE Phase)/OLE Phase.
- Any AEs leading to premature discontinuation of study drug in the BD/OLE phase.

7.1.5.2. Incomplete Dates

If the onset date of the AE is incomplete and the AE stop date is not prior to the first dosing date of study drug, then the month and year (or year alone if month is not recorded) of onset determine whether an AE is treatment-emergent. The event is considered treatment-emergent if both of the following 2 criteria are met:

- The AE onset is the same as or after the month and year (or year) of the first dosing date of study drug, and
- The AE onset date is the same as or before the month and year (or year) of the date corresponding to 30 days after the date of the last dose of study drug

An AE with completely missing onset and stop dates, or with the onset date missing and a stop date later than the first dosing date of study drug, will be considered to be treatment-emergent. In addition, an AE with the onset date missing and incomplete stop date with the same or later month and year (or year alone if month is not recorded) as the first dosing date of study drug will be considered treatment-emergent.

7.1.6. Summaries of Adverse Events and Deaths

Treatment-emergent (TE) AEs will be summarized based on the Safety Analysis Set for the BD Phase, and the LT analysis. TEAEs in the OLE Phase will be summarized based on the OLE Analysis Set. In LT analysis, TEAEs will be those included in BD Phase/OLE Phase summary.

The number and percentage of subjects who experienced at least 1 TEAE will be provided and summarized by SOC, PT, and treatment group. For other AEs described below, summaries will be provided by SOC, PT, and treatment group:

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

- All TEAEs leading to dose interruption of study drug
- All TEAEs leading to dose reduction of study drug (OLE Phase only)
- All AEs recorded between screening and prior to first dose of study drug

A brief, high-level summary of TEAEs, TEAEs with Grade 3 or Higher, TEAEs Related to Study Drug, TEAEs Related to Study Drug with Grade 3 or Higher, TE Serious AEs, TE Serious AEs Related to Study Drug, and TEAEs Leading to Premature Discontinuation of Study Drug will be provided by treatment group and by the number and percentage of subjects who experienced the above AEs. All deaths observed in the study will be also included in this summary.

Multiple events will be counted only once per subject in each summary. Adverse events will be summarized and listed first in alphabetic order of SOC, and then by PT in descending order of frequency of BD GS-9674 100 mg group within each SOC in the BD Phase/ total frequency within each SOC for the OLE Phase/ frequency of LT GS-9674 initially in 100 mg group in the long-term summary. For summaries by severity grade, the most severe grade will be used for those AEs that occurred more than once in an individual subject during the study.

In addition to the above summary tables, the following tables will be summarized by PT only, in descending order of frequency in the GS-9674 100 mg group in the BD Phase/ total frequency for the OLE Phase/ frequency of LT GS-9674 initially in 100 mg group in the long-term summary:

- All TEAEs
- TEAEs of Grade 3 or higher
- TE treatment-related AEs
- TE treatment-related AEs of Grade 3 or higher
- All TE SAEs
- All TE treatment-related SAEs
- In addition, data listings will be provided for the following:
- All AEs, indicating whether the event is treatment-emergent
- All AEs of Grade 3 or higher
- SAEs
- All TEAEs leading to Death

- AEs leading to premature discontinuation of study drug
- AEs leading to dose interruption of study drug
- AEs leading to dose reduction of study drug (OLE Phase only)

7.2. Laboratory Evaluations

Laboratory data collected during the study will be analyzed and summarized using both quantitative and qualitative methods. Summaries of laboratory data will be provided for the Safety Analysis Set/OLE Analysis Set and will include data collected up to the last dose of study drug plus 30 days in the BD Phase (and on or before the first dose date in the OLE Phase)/OLE Phase for subjects who have permanently discontinued study drug, or all available data at the time of the database snapshot for subjects who were ongoing at the time of an interim analysis. Data obtained at the ET or FU visit will be included in the by-visit summaries by their nominal visit ID in BD/OLE Phase, regardless of the relevant number of days to the last dose date. LT analysis will include data summarized in BD Phase/OLE Phase. Data obtained after the last dose of study drug plus 30 days in the BD (and prior to first dose date of OLE Phase)/OLE Phase will not be included in the evaluation of the TE laboratory abnormalities in the LT analysis. The analysis will be based on values reported in conventional units. When values are below the LOQ, they will be listed as such, and the closest imputed value will be used for the purpose of calculating summary statistics as specified in Section 3.7.

A by-subject listing for laboratory test results will be provided by subject ID number and visit in chronological order for hematology, serum chemistry, and urinalysis separately. Values falling outside of the relevant reference range and/or having a severity grade of 1 or higher on the CTCAE severity grade will be flagged in the data listings, as appropriate.

No formal statistical testing is planned.

7.2.1. Summaries of Numeric Laboratory Results

Descriptive statistics will be provided by treatment group for HOMA-IR, HbA1c, albumin, creatinine, fasting insulin, fasting glucose, prothrombin time, INR, WBC, neutrophils, lymphocytes, hemoglobin, platelets as follows:

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

in the BD Phase, the OLE Phase and the LT analysis, separately.

A baseline laboratory value will be defined as the last measurement obtained on or prior to the date/time of first dose of study drug. Change from baseline to a postbaseline visit will be defined as the visit value minus the baseline value. The mean, median, Q1, Q3, minimum, and maximum

values will be displayed to the reported number of digits; SD values will be displayed to the reported number of digits plus 1.

Median (Q1, Q3) of the observed values for HOMA-IR, HbA1c, albumin, creatinine, fasting insulin, fasting glucose, prothrombin time, INR, WBC, neutrophils, lymphocytes, hemoglobin, platelets will be plotted using a line plot by treatment group and visit.

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

7.2.2. Graded Laboratory Values

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

For the baseline ALP, ALT, AST, total bilirubin toxicity grades at the BD Phase, the CTCAE version 4.03 will be used to assign grades to the derived average values. See Appendix 2 for the link to CTCAE 4.03.

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 in the BD Phase (and on or before the first dose of the OLE Phase)/OLE Phase for subjects who permanently discontinued study drug, or the last available date in the database snapshot for subjects who were still on treatment at the time of an interim analysis. LT analysis will include data summarized in BD Phase/OLE Phase. Data obtained after the last dose of study drug plus 30 days in the BD (and prior to first dose date of OLE Phase)/OLE Phase will not be included in the evaluation of the TE laboratory abnormalities in the LT analysis. If the relevant baseline laboratory value is missing, any abnormality of at least Grade 1 observed within the time frame specified above will be considered treatment-emergent.

7.2.2.2. Treatment-Emergent Marked Laboratory Abnormalities

Treatment-emergent marked laboratory abnormalities are defined as values that increase from baseline by at least 3 toxicity grades at any postbaseline time point, up to and including the date of the last dose of study drug plus 30 days in BD Phase (and on or before the first dose of OLE Phase)/OLE Phase for subjects who permanently discontinued study drug or the last available date in the database snapshot for subjects who were still on treatment at the time of an interim analysis. LT analysis will include data summarized in BD Phase/OLE Phase. Data obtained after the last dose of study drug plus 30 days in the BD (and prior to first dose date of OLE Phase)/OLE Phase will not be included in the evaluation of the TE laboratory abnormalities in the LT analysis. If the relevant baseline laboratory value is missing, any Grade 3 or 4 values observed within the timeframe specified above will be considered treatment-emergent marked abnormalities.

7.2.2.3. Summaries of Laboratory Abnormalities

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

- Graded laboratory abnormalities
- Grade 3 or 4 laboratory abnormalities
- Marked laboratory abnormalities

For all summaries of laboratory abnormalities, the denominator is the number of subjects with nonmissing postbaseline values up to 30 days after last dose date in the study phase reported. LT analysis will include data summarized in BD Phase/OLE Phase. Data obtained after the last dose of study drug plus 30 days in the BD (and prior to first dose date of OLE Phase)/OLE Phase will not be included in the evaluation of the TE laboratory abnormalities in the LT analysis.

A by-subject listing of treatment-emergent Grade 3 or 4 laboratory abnormalities will be provided by subject ID number and visit in chronological order. This listing will include all test results that were collected throughout the study for the lab test of interest, with all applicable severity grades or abnormal flags displayed.

7.2.3. Liver-related Laboratory Evaluations

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

Subjects meet criteria for liver-related events:

- For subjects with normal baseline ALT (AST):
  - ALT (AST) > 3 × ULN
  - Total bilirubin > 2 × ULN
  - INR > 1.5 (except for subjects on anticoagulant therapy)
- For subjects with elevated ALT (AST) (≥ upper limit of normal [ULN]) at study start:
  - ALT (AST) > 2 × baseline
  - Total bilirubin > 2 × ULN
  - INR > 1.5 (except for subjects on anticoagulant therapy)

Subjects meet criteria for drug withheld:

- ALT (AST) > 5 × baseline
- ALT (AST) > 10 × ULN
- ALT (AST) > 3 × baseline with total bilirubin > 2 × ULN
- ALT (AST) > 3 × baseline with total bilirubin > 1.5 × baseline
- ALT (AST) > 3 × baseline with INR > 1.5 (except for subjects on anticoagulant therapy)
- ALT (AST) > baseline with total bilirubin > 2 × ULN, and INR > 1.5 (except for subjects on anticoagulant therapy)
- ALT (AST) > baseline with total bilirubin > 1.5 × baseline, and INR > 1.5 (except for subjects on anticoagulant therapy)

The summary will include data from all postbaseline visits up to 30 days after the last dose of study drug in the BD Phase (and on or before the first dose of the OLE Phase)/OLE Phase. LT analysis will include data summarized in BD Phase/OLE Phase. Data obtained after the last dose of study drug plus 30 days in the BD (and prior to first dose date of OLE Phase)/OLE Phase will not be included in the evaluation of the TE laboratory abnormalities in the LT analysis. For individual laboratory tests, subjects will be counted once based on the most severe postbaseline values. For the criteria of ALT (AST) and total bilirubin, INR, subjects will be counted once when the criteria are met at the same postbaseline visit date. The denominator is the number of subjects in the Safety Analysis Set/OLE Analysis Set who have nonmissing postbaseline values of all relevant tests at the same postbaseline visit date in the corresponding baseline group. A listing of subjects who met at least 1 of the above criteria will be provided.

7.3. Vital Signs

Descriptive statistics will be provided for vital signs (systolic and diastolic blood pressure [mmHg], pulse [beats/min], respiratory rate [breath/min] and temperature [°C]) in the BD Phase, the OLE Phase and the LT analysis according to treatment groups in Section 3.2 as follows:

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

A baseline value will be defined as the last available value collected on or prior to the date/time of first dose of study drug in the reporting phase. Change from baseline to a postbaseline visit will be defined as the postbaseline value minus the baseline value. Vital signs measured at unscheduled visits will be included for the baseline value selection.

In the case of multiple values in an analysis window, data will be selected for analysis as described in Section 3.8.3. No formal statistical testing is planned.

A by-subject listing of vital signs will be provided by subject ID number and visit in chronological order.

7.4. Prior and Concomitant Medications

Medications collected at screening and during the study will be coded using the current version of the World Health Organization (WHO) Drug dictionary.

7.4.1. Prior Medications

Prior medications are defined as any medications taken before a subject took the first study drug.

Prior medications will be summarized by preferred name using the number and percentage of subjects for each treatment group and overall in BD Phase. A subject reporting the same medication more than once will be counted only once when calculating the number and percentage of subjects who received that medication. The summary will be ordered by preferred term in order of descending overall frequency. For drugs with the same frequency, sorting will be done alphabetically.

For the purposes of analysis, any medication with a start date prior to the first dose date of study drug will be included in the prior medication summary regardless of when the stop date is. If a partial start date is entered the medication will be considered prior unless the month and year (if day is missing) or year (if day and month are missing) of the start date are after the first dose date. Medications with a completely missing start date will be included in the prior medication summary, unless otherwise specified.

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

7.4.2. Concomitant Medications

Concomitant medications are defined as medications taken while a subject took study drug. Use of concomitant medications will be summarized by preferred name using the number and percentage of subjects for each treatment group. A subject reporting the same medication more than once will be counted only once when calculating the number and percentage of subjects who received that medication. The summary will be ordered by preferred term in descending frequency in the GS-9674 100 mg group (BD Phase/LT analysis), and in the GS-9674 Total group (OLE Phase). For drugs with the same frequency, sorting will be done alphabetically.

For the purposes of analysis, any medications with a start date prior to or on the first dose date of study drug of the study phase and continued to be taken after the first dose date, or started after the first dose date but prior to or on the last dose date of study drug of the study phase will be considered concomitant medications. Medications started and stopped on the same day as the first dose date or the last dose date of study drug will also be considered concomitant. Medications with a stop date prior to the date of first dose date of study drug or a start date after

the last dose date of study drug will be excluded from the concomitant medication summary. If a partial stop date is entered, any medication with the month and year (if day is missing) or year (if day and month are missing) prior to the date of first study drug administration will be excluded from the concomitant medication summary. If a partial start date is entered, any medication with the month and year (if day is missing) or year (if day and month are missing) after the study drug stop date will be excluded from the concomitant medication summary. Medications with completely missing start and stop dates will be included in the concomitant medication summary, unless otherwise specified. Summaries will be based on the Safety Analysis Set/OLE Analysis Set. No formal statistical testing is planned.

All prior and concomitant medications (other than per-protocol study drugs) will be provided in a by-subject listing sorted by subject ID number and administration date in chronological order.

7.5. Electrocardiogram Results

ECG analysis results are intended to identify meaningful abnormalities. If potential abnormalities of interest are identified, further analyses may be conducted.

A shift table of the investigators' assessment of ECG results at Week 12 of the BD Phase compared with baseline values will be presented by treatment group using the following categories: normal; abnormal, not clinically significant; abnormal, clinically significant; or missing. The number and percentage of subjects in each cross-classification group of the shift table will be presented. Subjects with a missing value at baseline or postbaseline will not be included in the denominator for percentage calculation. No formal statistical testing is planned.

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

7.6. Other Safety Measures

7.6.1. Partial Mayo Score

The partial Mayo score is a survey score for the assessment of IBD that considers stool frequency and rectal bleeding. At each study visit, two sub score components will be reported:

- Stool frequency sub score: a numeric value ranging from 0 to 3 (where 0 = normal for the patient, 1 = 1 − 2 stools more than normal, 2 = 3 − 4 stools more than normal, 3 = 5 or more stools more than normal);

- Rectal bleeding sub score: a numeric value ranging from 0 to 3 (where 0 = no blood seen, 1 = streaks of blood with stool less than half the time, 2 = obvious blood with stool most of the time, 3 = blood alone passes).

Partial Mayo score will be calculated as the sum of the above two sub scores. If one or both sub scores are missing, partial Mayo score will be considered missing.

Partial Mayo score and its two components will be reported for subjects with IBD history based on the Safety Analysis Set for the BD Phase, and the LT analysis. Partial Mayo score in the OLE Phase will be summarized based on the OLE Analysis Set.

Descriptive statistics will be provided for partial Mayo score in the BD Phase, the OLE Phase and the LT analysis according to treatment groups in Section 3.2 as follows:

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

A baseline value will be defined as the last available value collected on or prior to the date/time of first dose of study drug in the BD Phase. Change from baseline to a postbaseline visit will be defined as the postbaseline value minus the baseline value. Partial Mayo scores calculated at unscheduled visits will be included for the baseline value selection.

For each subject, the nadir will be determined as the minimum score from baseline to the last available visit; change from nadir will be calculated only for visits that are after the earliest visit with the nadir value. Nadir values will be summarized using descriptive statistics.

Subjects with change from nadir at any visit ≥ 2 points and within 30 days of the last dose in each phase will be identified. Number and percent of these subjects will be reported. Maximum change from nadir for these subjects will be summarized.

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 available partial Mayo scores, its two components, nadir and change from nadir will be provided by subject ID number and visit in chronological order. Any subject with a history of IBD who experiences at least a 2-point increase from nadir in the partial Mayo score during the course of the study within 30 days of the last dose will be flagged in the listing.

7.7. Changes From Protocol-Specified Safety Analyses

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

8. PHARMACOKINETIC (PK) ANALYSES

8.1. PK Sample Collection

A single predose PK blood sample (Sparse PK Sampling) will be collected at Week 1, 2, 4, 8, and 12 in BD Phase for all subjects.

PPD

A population PK model will be developed to characterize the PK of GS-9674 and its metabolites (as applicable). Data from this study (single PKPPD) will 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

PPD

8.2.1. Estimation of PK Parameters

PK parameters will be estimated using Phoenix WinNonlin® software using standard noncompartmental methods. The linear up/log down 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. Predose samples may also be used as t=24 hr postdose samples for the purposes of PK parameter generation, as appropriate.

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. PK Parameters

PPD

PPD

The analytes and parameters presented in Table 8-2 will be used to evaluate the PK objectives of the study. The PK parameters to be estimated in this study are listed and defined in the PK Abbreviations section.

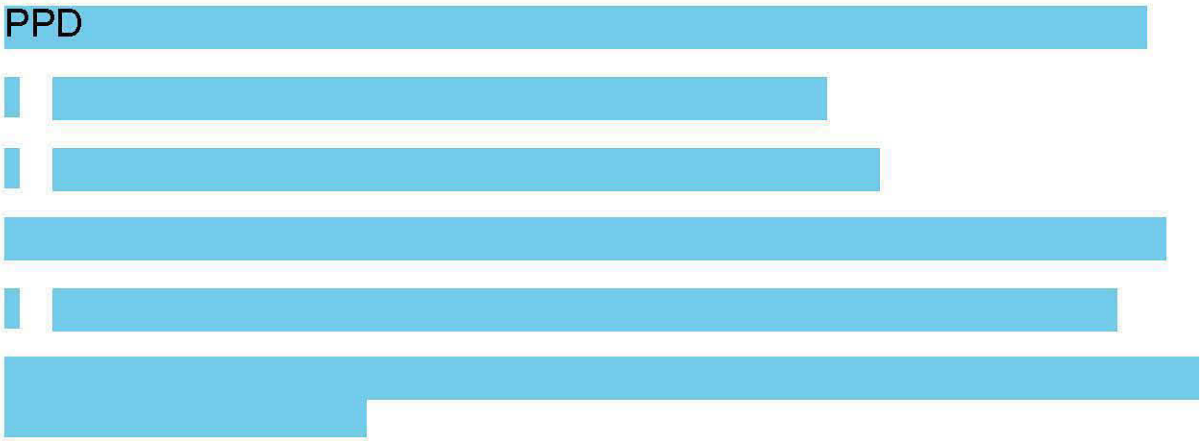
Table 8-2. PK Parameters for Each Analyte

Analyte	Parameters
GS-9674	AUC_{last}, AUC_{tau}, C_{max}, T_{max}, C_{last}, T_{last}, C_{tau}, λz, CLss/F, and $t_{1/2}$
GS-716070	AUC_{last}, AUC_{tau}, C_{max}, T_{max}, C_{last}, T_{last}, C_{tau}, λz, and $t_{1/2}$

Individual subject concentration data and individual subject PK parameters for GS-9674 and its metabolites (as appropriate), will be listed and summarized using descriptive statistics by treatment. Summary statistics (n, 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 by treatment. 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.

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 listings will be provided:

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

- Individual data on determination of plasma half-life and corresponding correlation coefficient

8.3. PK Analyses Related to Sparse PK Sampling

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 corresponding PK data listing described in Section 8.2.2.

9. REFERENCES

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Goff DC, Jr., Lloyd-Jones DM, Bennett G, Coady S, D'Agostino RB, Gibbons R, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2014;129 (25 Suppl 2):S49-73.

Jacoby A, Rannard A, Buck D, Bhala N, Newton JL, James OF, et al. Development, validation, and evaluation of the PBC-40, a disease specific health related quality of life measure for primary biliary cirrhosis. Gut 2005;54 (11):1622-9.

Kim WR, Therneau TM, Wiesner RH, Poterucha JJ, Benson JT, Malinchoc M, et al. A revised natural history model for primary sclerosing cholangitis. Mayo Clin Proc 2000;75 (7):688-94.

10. SOFTWARE

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

11. SAP REVISION

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

12. APPENDICES

Appendix 1. Study Procedures Table

		Blinded Study Phase Treatment Weeks (±3 days)							OLE Weeks (±3 days weeks 1-12 and ±5 days weeks 24-96)	
	Screening [a]	Baseline (Day 1)	Week 1	Week 2	Week 4	Week 8	Week 12 /ET [b]	Blinded Study Phase follow-up visit [c] (±5 days)	OLE Baseline/Day 1, Weeks 1, 2, 4, 8, 12, 24, 36, 48, 60, 72, 84, 96/ET [b]	OLE follow-up [d]
Subject Fasting		X	X	X	X	X	X		X	
Written Informed Consent[e]	X									
Review Inclusion/Exclusion Criteria	X	X								
Medical History	X									
Partial Mayo Score[f]	X	X	X	X	X	X	X	X	X	X
Pruritus VAS &5D-Itch [g]		X	X	X	X	X	X	X	X	X
QoL SF-36, PSC-PRO & PBC-40[g]		X					X	X	X	
Symptom-directed PE[h]	X	X	X	X	X	X	X	X	X	X
Vital Signs[i]	X	X	X	X	X	X	X	X	X	X
Height and weight[j]	X	X	X	X	X	X	X	X	X	X
Chemistry	X	X	X	X	X	X	X	X	X	X
Hematology	X	X	X	X	X	X	X	X	X	X
Coagulation Panel	X	X	X	X	X	X	X	X	X	X

		Blinded Study Phase Treatment Weeks (±3 days)							OLE Weeks (±3 days weeks 1-12 and ±5 days weeks 24-96)	
	Screening [a]	Baseline (Day 1)	Week 1	Week 2	Week 4	Week 8	Week 12 /ET [b]	Blinded Study Phase follow-up visit [c] (±5 days)	OLE Baseline/Day 1, Weeks 1, 2, 4, 8, 12, 24, 36, 48, 60, 72, 84, 96/ET [b]	OLE follow-up [d]
Cirrhosis Assessments	X									
Lipid Profile		X	X		X	X	X	X	X	X
C-Peptide, Hemoglobin A1C and Insulin		X					X			
Blood for Biomarkers [k]	X	X	X		X		X	X	X	
Single PK and PD Sampling		X[l]	X	X	X	X	X			
HIV-1, HBV and HCV Serology	X									
Pregnancy Test[m]	X	X	X		X	X	X	X	X	X
Serum FSH[n]	X									
PPD										
12- lead ECGs		X					X			
Fibroscan[p]		X					X			
MRE[q]		X							X	
MRCP[r]		X							X	

		Blinded Study Phase Treatment Weeks (±3 days)							OLE Weeks (±3 days weeks 1-12 and ±5 days weeks 24-96)	
	Screening [a]	**Baseline (Day 1)**	**Week 1**	**Week 2**	**Week 4**	**Week 8**	**Week 12 /ET** [b]	**Blinded Study Phase follow-up visit** [c] **(±5 days)**	**OLE Baseline/Day 1, Weeks 1, 2, 4, 8, 12, 24, 36, 48, 60, 72, 84, 96/ET** [b]	**OLE follow-up** [d]
Urine drug screening	X									
Urine collection (Biomarkers)[s]		X	X		X		X	X	X	
Stool collection (Biomarkers)[t]		X					X	X	X	
PPD										
Dispense GS-9674/ PTM GS-9674[v]		X			X	X			X	
Concomitant Medications	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X
Take GS-9674/ PTM GS-9674 Tablets		X – Daily (Baseline/ Day 1 to Week 12)[w]							X-Daily (OLE Baseline/ Day 1 to Week 96)	

a The visit window may be extended under special circumstances with explicit approval of the Medical Monitor. Subjects who fail to meet eligibility criteria due to an abnormal laboratory result may undergo re-testing of the abnormal analyte during the screening window. This will be done at the discretion of the investigator and also with prior approval of the Medical Monitor.

b Blinded Study Phase subjects discontinuing the study at any time for any reason (Early Termination – ET) should complete the procedures listed for the Week 12/ Visit AND the follow-up visit. OLE Phase subjects discontinuing the study at any time for any reason (Early Termination – ET) should complete the procedures listed for the Week 96/ Visit AND the follow-up visit if possible.

c After completing 12 weeks of treatment in the Blinded Study Phase, subjects will return for the follow-up visit 4 weeks post the last dose of the study drug and at that time they can begin their OLE Phase. Follow-up visit for Blinded Study Phase and Baseline/Day 1 OLE visit can occur on the same day if convenient. If OLE Baseline/Day 1 and Blinded study follow-Up visit is on the same day subjects should only complete OLE Baseline /Day 1 assessments.

d Follow-up visit should be completed during the Blinded Study Phase as well as the OLE Phase.

e Obtain written informed consent before initiation of any screening procedure.

f Phone follow-up every 4 weeks after OLE Week 12, (OLE Week 16, 20, 28, 32, 40, 44, 52, 56, 64, 68, 76, 80, 88 and 92).
g QoL questionnaires and Pruritus assessments should be completed prior to any study procedures being performed and prior to the subject seeing a health care provider. Refer to the Study Reference Binder for guidance on QoL questionnaire administration. During OLE, QoL questionnaires are required at OLE Baseline/Day 1, Weeks 4, 12 and every 12 weeks thereafter.
h Complete PE at screening and symptom-directed PE for other visits. The focus of a symptom-driven physical examination will be determined by the investigator based on subject complaint.
i Vital signs include (heart rate, systolic and diastolic blood pressure, respiratory rate, and body temperature)
j Height should be collected at Screening and Baseline/Day 1 only. Weight should be collected at all visits. Refer to the Study Reference Binder for specific instructions on how weight should be measured.
k Biomarker analyses include, but are not limited to, the tests listed in Section 6.12.1 of the protocol. Some of the blood collected for biomarkers may be stored for future testing.
l PD sampling only at Baseline/Day 1.
m Females of childbearing potential only (see Appendix 4 of the protocol). Serum pregnancy tests at Screening. Urine pregnancy test at all other visits, except Blinded Study Phase Week 2 and OLE Weeks 1, and 2.
n Only required for some female subjects – see Appendix 4 of the protocol.
PPD
p Subject should be in fasted state for FibroScan® collection. Refer to the study reference binder for further details. If FibroScan® is not available at a site the test may be omitted.
q Should be in a fasted state for MRE scan. Refer to study reference binder for further details. If MRE is not available at a site the test may be omitted. MRE scan should be performed at Blinded Study Phase Baseline/Day 1 and OLE Weeks 48 and 96.
r MRCP is to be performed at Blinded Study Phase Baseline/Day 1 and OLE Weeks 48 and 96. Refer to study reference binder for further details.
s Urine Biomarker sample collection at Blinded Study Phase Baseline/Day 1, week 1, weeks 4, 12 and at the Follow up and Early term visits. Urine Biomarker sample collection during OLE at OLE Baseline/Day 1, Weeks 24, 48, 72 and 96 only.
t Stool sample collection at Blinded Study Phase Baseline/Day 1, Week 12 and at the Follow up and Early term visits. Stool sample collection during OLE at OLE Baseline/Day 1, Week 48 and Week 96 visit
PPD
v Study drug will be assigned via the IWRS system every 4 weeks from Baseline/Day 1 through Week 8 in Blinded Study Phase and at OLE Baseline/Day 1, Weeks 1, 4, 8 12 and every 12 weeks thereafter.
w Subjects to self-administer the study drug at the investigative site at the conclusion of the Blinded Study Phase Baseline/Day 1 and Week 12 visit.

Appendix 2. CTCAE Grading Scale for Severity of Adverse Events and Laboratory Abnormalities

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

Appendix 3. Programming Specifications

FibroSURE/FibroTest® Calculation:

Step-1 formula	f5 = 4.467 × Log[α_2-macroglobulin(g/L)] – 1.357 × Log[Haptoglobin (g/L)] + 1.017 × Log[GGT(U/L)] + 0.028 × [Age (year)] + 1.737 × Log [Total Bilirubin (umol/L)] – 1.184 × [ApoA1 (g/L)] + 0.301 × Sex (female = 0, male = 1) – 5.540
Step-2 formula	FibroSURE/FibroTest® Score = 1/(1+exp^(-f5))
Note	• In the formula, SI value and units should be applied. • The Log function in the formula is with base 10. • FibroSURE/FibroTest® score should be calculated from the parameters from the same blood draw • Age is when the blood draw was taken

For subject with Gilbert's syndrome or hemolysis according to the medical history page at screening, the FibroSURE/FibroTest® score will be calculated using Direct Bilirubin instead of Total Bilirubin in above formula throughout the study.

HOMA-IR Calculation:

HOMA-IR = fasting glucose (mg/dL) × fasting insulin (muIU/mL) / 405. Keep 2 decimal places. The lab parameters need to be measured from the same blood draw.

Pooled Cohort Risk Score:

No.	Parameters	Coefficient			
		Female		Male	
		White or Other	African America	White or Other	African America
1	ln Age (y)	–29.799	17.114	12.344	2.469
2	ln Age, Squared	4.884	N/A	N/A	N/A
3	ln Total Cholesterol (mg/dL)	13.540	0.940	11.853	0.302
4	ln Age × ln Total Cholesterol	–3.114	N/A	–2.664	N/A
5	ln HDL-C (mg/dL)	–13.578	–18.920	–7.990	–0.307
6	ln Age × ln HDL-C	3.149	4.475	1.769	N/A
7	ln Treated Systolic BP (mm Hg)	2.019	29.291	1.797	1.916
8	ln Age × ln Treated Systolic BP	N/A	–6.432	N/A	N/A
9	ln Untreated Systolic BP (mm Hg)	1.957	27.820	1.764	1.809
10	ln Age × ln Untreated Systolic BP	N/A	–6.087	N/A	N/A
11	Current Smoker (1=Yes, 0=No)	7.574	0.691	7.837	0.549
12	ln Age × Current Smoker	–1.665	N/A	–1.795	N/A
13	Diabetes (1=Yes, 0=No)	0.661	0.874	0.658	0.645
A	Baseline Survival	0.9665	0.9533	0.9144	0.8954
B	Individual Sum = ∑(coefficient*parameter)	For each individual patient, individual sum is summation of product of each parameter and its corresponding coefficient for that sex-race group for all parameters listed above (#1 -#13). *Note: N/A indicates that the specific coefficient is not available thus the corresponding parameter will not be included in calculation.*			
C	Population Mean	–29.18	86.61	61.18	19.54
D	Pooled Cohort Risk Score	= B − C = Individual Sum – Population Mean			
E	Pooled Cohort Risk = Estimated probability of a first hard ASCVD event within 10 years	= 1 – A ^ exp(B-C), ie, = 1 − Baseline Survival ^ exp (Individual Sum- Population Mean)			

ASCVD = atherosclerotic cardiovascular disease; BP = blood pressure; HDL-C = high-density lipoprotein cholesterol; ln = natural logarithm. Age is the actual age when the lab parameters are collected for the visit. Total Cholesterol and HDL-C, Systolic BP are assessed at a same visit when risk score are to be reported, where total cholesterol and HDL-C should be obtained on the same day. Smoker, and diagnosis of Diabetes are collected at Screening/Baseline on the page of Medical History. Status of hypertension treatment is determined based on prior and concomitant medications taken at baseline of the BD Phase for analysis for the visits in BD Phase, and on the date when the blood pressure is collected for the visit analyzed in the OLE Phase. Round Pooled Cohort Risk Score to 0.001.

Mayo Risk Score:

Mayo Risk Score R = 0.03 Age (years) + 0.54 Ln total bilirubin (mg/dL) + 0.54 Ln AST (U/L) +1.24 variceal bleeding (0/1) – 0.84 albumin (g/dL).

Keep 2 decimal places. The lab parameters need to be measured from the same blood draw. Age should be the actual age at the date when lab values are taken. Status of variceal bleeding should also be decided on the lab date. If a subject has a history or new onset of variceal bleeding, the variceal bleeding variable will be set to 1 and carried over for future visits; otherwise 0.

5D-Itch Score:

5D-Itch contains a total of 5 questions with each ranging from 1 to 5. It includes 16 potential locations of itch, including 15 body part items and one point of contact with clothing or bandages. Single-item domain scores (duration, degree and direction) are equal to the value indicated below the response choice (range 1–5). The score for the disability domain is achieved by taking the highest score on any of the four items (sleep, leisure/social, housework/errands, and work/school). For the distribution domain, the number of affected body parts is tallied (potential sum 0 – 16, where body parts with missing responses are considered not affected and assigned a value of zero for summation) and the sum is sorted into five scoring bins: sum of 0 – 2 = score of 1, sum of 3 – 5 = score of 2, sum of 6 – 10 = score of 3, sum of 11 – 13 = score of 4, and sum of 14 – 16 = score of 5. The scores of each of the five domains are achieved separately. For subjects who have entered into OLE phase, the missing value on OLE day 1 for a domain is imputed using the corresponding last non-missing value in BD phase. The 5D-Itch total score is then the summation of the five domain scores. 5D-Itch scores can potentially range between 5 (no pruritus) and 25 (most severe pruritus) {Elman et al 2010}.

PBC-40 (for PSC Subjects):

PBC-40 scores are calculated using subject responses to 40 questions in the questionnaire. There are a total of 6 domains in the following across the 40 questions.

- Fatigue
- Emotion
- Social function
- Cognitive function
- General symptoms
- Itching

Analysis is by domain, with the scoring explained in the coded-PBC-40. Data should be considered by domain rather than in terms of a cumulative PBC-40 score. If data are missing from a domain (typically missed or duplicated answers) the whole domain should be discarded if ≥ 50% of items are missing. If > 50% of responses are present then the median value for the completed items in the domain should be ascribed to the missing item {Jacoby et al 2005}.