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 Nonalcoholic Steatohepatitis (NASH)
Name of Test Drug:	GS-9674
Study Number:	GS-US-402-1852
Protocol Version (Date):	Amendment 2 (24 January 2017)
Analysis Type:	Interim Analysis and Final Analysis
Analysis Plan Version:	Version 1.0
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Analysis Plan Author:	PPD

CONFIDENTIAL AND PROPRIETARY INFORMATION

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
ATC	anatomical therapeutic chemical
AUC	area under the concentration
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
CK18	cytokeratin 18
CLDQ	chronic liver disease questionnaire
CRF	case report form
CRP	C-reactive protein
CSR	clinical study report
CTCAE	Common Toxicity Criteria for Adverse Events
DDE	double-double-echo
DILI	drug induced liver injury
DMC	data monitoring committee
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
ELF	enhanced liver fribrosis
ET	early termination
EOT	end of treatment
FAS	Full Analysis Set
FGF19	firbroblast growth factor 19
FU	follow up
GGT	gamma glutamyl transferase
GSI	Gilead Sciences, Inc.
HbA1c	hemoglobin A1c
HCV	hepatitis C virus
HDL	high-density lipoprotein
HDL-C	HDL-cholesterol
HLT	high level term
HLGT	high level group term

HOMA-IR	homeostasis model assessment of insulin resistance
ID	identification
IND	Investigational New Drug (Application)
INR	international normalized ratio
IXRS	interactive voice/web response system
LDH	lactate dehydrogenase
LDL-C	low-density lipoprotein cholesterol
LLT	lower level term
LOQ	limit of quantitation
ME	multiple-echo
MedDRA	medical dictionary for regulatory activities
NASH	nonalcoholic steatohepatitis
PD	pharmacodynamics
PE	physical examination
PK	pharmacokinetic
PT	preferred term
Q1	first quartile
Q3	third quartile
QoL	quality of life
RBC	red blood cell
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
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
ULN	upper limit of normal
ULOQ	upper limit of quantitation
VLDL-C	very low density lipoprotein-cholesterol
WBC	white blood cell
WHO	World Health Organization
WPAI	work productivity and activity impairment questionnaire

PHARMACOKINETIC ABBREVIATIONS

AUC_{last}	area under the concentration versus time curve from time zero to the last quantifiable concentration
AUC_{tau}	area under the concentration versus time curve over the dosing interval
C_{last}	last observed quantifiable concentration of the drug
C_{max}	maximum observed concentration of drug
C_{tau}	observed drug concentration at the end of the dosing interval
CLss/F	apparent oral clearance after administration of the drug: 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 interim analysis at Week 12 and the final analysis at Week 24 to be included in the clinical study report (CSR) for Study GS-US-402-1852. The formal interim analysis will be performed when all subjects have completed the Week 12 assessment or prematurely discontinued from the study. The purpose of this interim analysis is administrative. As such, no stopping criteria are listed in Section 2 of this SAP. The final analysis will be performed when all subjects have completed all assessments as defined in the protocol or prematurely discontinued from the study and the database has been locked.

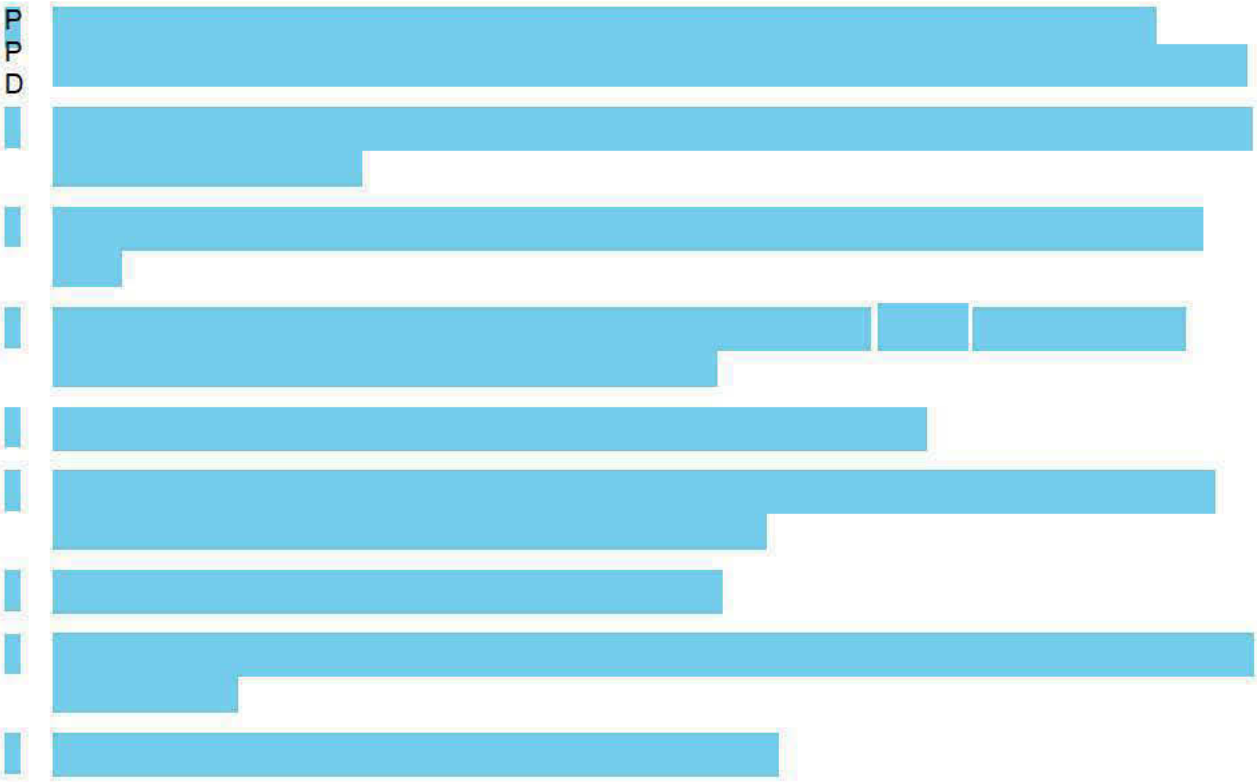
This SAP is based on the study protocol Amendment 2 dated 24 January 2017 and the electronic case report form (eCRF). The SAP will be finalized before database finalization. Any changes made after the finalization of the SAP will be documented in the CSR.

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 NASH.

The exploratory objectives of this study are as follows:

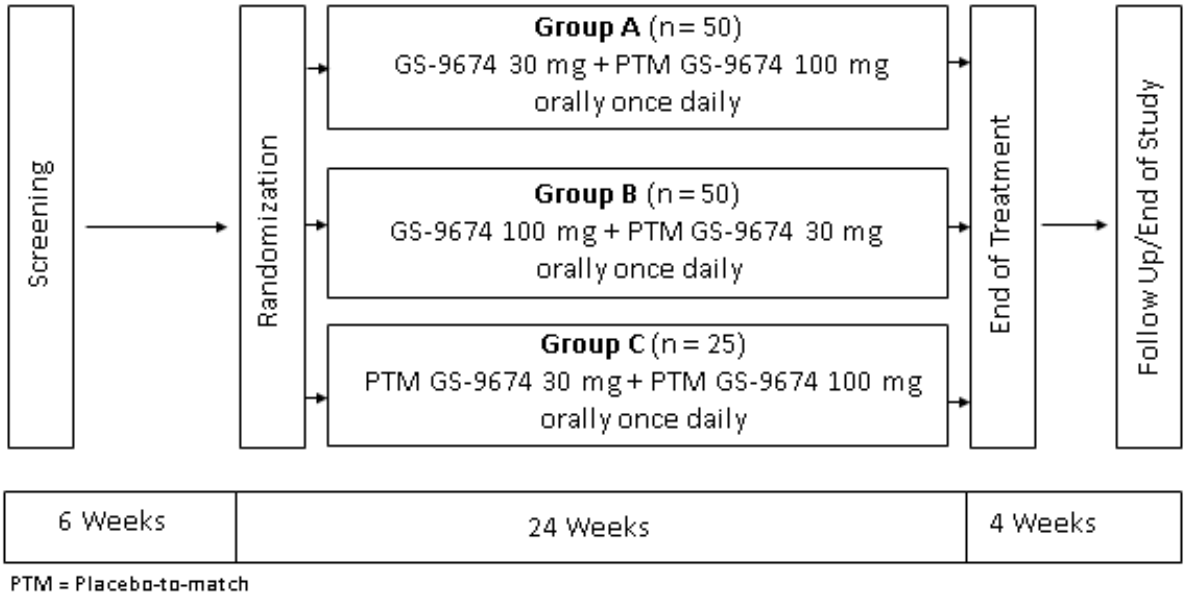


1.2. Study Design

This is a Phase 2, randomized, double-blind, placebo-controlled study designed to evaluate the safety, tolerability, and efficacy of GS-9674 in subjects with NASH. To be eligible to participate, subjects must have evidence of hepatic steatosis and increased liver stiffness as assessed by MRI-PDFF and MRE respectively, or a historical liver biopsy consistent with NASH and noncirrhotic fibrosis. Any subject with a history of decompensated liver disease, including ascites, hepatic encephalopathy, or variceal bleeding will be ineligible.

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

Figure 1-1. Overall Study Design



Subjects meeting the study's entry criteria will be randomly assigned in a 2:2:1 ratio to 1 of 3 different treatment groups (A, B, and C) as shown in Figure 1-1. Randomization will be stratified by the presence or absence of diabetes mellitus as determined by medical history, use of medication for indication of diabetes mellitus, or based on screening lab values if previously undiagnosed (ie, hemoglobin A1c ≥ 6.5% OR fasting plasma glucose ≥ 126 mg/dL).

Study drug will be administered for a total of 24 weeks from the Baseline/Day 1 visit up to and including the Week 24 visit.

After the Screening period and a randomization visit at Baseline/Day 1, study visits will occur on Weeks 1, 4, 8, 12, 16, 20, 24 and a Follow-Up visit 4 weeks after the last dose of study drug. At minimum, vital sign measurements, symptom-driven physical examinations (PEs), safety laboratory tests (blood chemistry, hematology, coagulation panel, and lipid profile), and review of adverse events (AEs) and concomitant medications (CMs) will be done at every visit. Refer to Appendix 1 for details.

1.3. Sample Size and Power

Due to the exploratory nature of this study, no formal power calculations were used to determine sample size. The number of subjects was chosen based on clinical experience with other similar proof-of-concept studies. However, assuming that 4% of subjects in the placebo group (N=25) and 32% in the GS-9674 100 mg group (N=50) have a ≥ 30% reduction in MRI-PDFF at Week 24, this sample size will provide 80% power to detect the difference based on a two-sided Fisher's exact test at a significance level of 0.05.

2. TYPE OF PLANNED ANALYSIS

2.1. Interim Analyses

2.1.1. Data Monitoring Committee Safety Analyses

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

The DMC will convene once 20 subjects have been enrolled and will meet every 3 to 4 months thereafter to monitor the study for safety events. The DMC will meet on an ad hoc basis if there are at least 3 Grade ≥ 3 serious, treatment-related Common Terminology Criteria for Adverse Events (CTCAE) observed in the study. In the event of two similar Grade 4-CTCAE treatment-related adverse events or one Grade 5-CTCAE treatment-related adverse event, the DMC will review the data and advise the sponsor regarding stopping or continuing the study. The DMC may also provide recommendations as needed regarding study design.

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.

2.1.2. Interim Analysis at Week 12

After all subjects have completed the Week 12 assessments or prematurely discontinued from the study an interim analysis evaluating the efficacy of GS-9674 will be performed. A data cut will be conducted to include only data up to the date of the last subject last visit for this particular time point. Details will be provided in the data cut plan for the Week 12 Interim Analysis. Study blinding will not be broken for the study management team (SMT), but a selected small number of Gilead personnel will be provided with unblinded results for decision-making purposes.

2.2. Final Analysis

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

3. GENERAL CONSIDERATIONS FOR DATA ANALYSES

Analysis results will be presented using descriptive statistics. For categorical variables, the number and percentage of subjects in each category will be presented; for continuous variables, the number of subjects (n), mean, standard deviation (SD), median, first quartile (Q1), third quartile (Q3), minimum, and maximum will be presented.

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

By-subject listings will be presented for all subjects in the Safety Analysis Set 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 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. 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 by treatment group.

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

3.1.1. All Randomized Analysis Set

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

3.1.2. Full Analysis Set

The Full Analysis Set (FAS) includes all subjects who were randomized 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. 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 value reported by the PK laboratory. This is the primary analysis set for all PK analyses. Within the PK Analysis Set,

those subjects with PK exposure data successfully derived from the population PK modeling will be included in the analyses related to PK exposure.

3.1.5. Pharmacokinetic Substudy Analysis Set

PPD

3.2. Subject Grouping

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

For analyses, subjects will be grouped as follows:

1) GS-9674 100 mg: This group includes all subjects who received GS-9674 100 mg;

2) GS-9674 30 mg: This group includes all subjects who received GS-9674 30 mg;

3) GS-9674 Pooled: This group includes all subjects who received GS-9674 100 mg or GS-9674 30 mg;

4) Placebo: This group includes all subjects who received Placebo.

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 (IXRS) in a 2:2:1 ratio using a stratified randomization schedule. Stratification will be based on the presence or absence of diabetes mellitus at baseline.

If there are discrepancies in stratification factor values between the IXRS and the clinical database, the values recorded in the clinical database will be used for analyses. The determination of diabetes mellitus from the clinical database is determined by medical history, use of medication for indication of diabetes mellitus, or based on lab values (either Screening or Baseline/Day 1 value prior to first dosing) if previously undiagnosed (ie, hemoglobin A1c $\geq$ 6.5% or fasting glucose $\geq$ 126 mg/dL).

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:

- presence of diabetes mellitus
- absence of diabetes mellitus

3.5. Multiple Comparisons

Adjustments for multiplicity will not be made because no formal statistical 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. Exceptions are presented in this document.

For missing MRI-PDFF sequence(s), imputation rules are specified in Section 6.2.3. 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 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).

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 LOQ at postbaseline time points.

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

- If at least 1 subject has a concentration value of BLQ for the time point, the minimum value will be displayed as "BLQ."
- If more than 25% of the subjects have a concentration data value of BLQ for a given time point, the minimum and Q1 values will be displayed as "BLQ."
- If more than 50% of the subjects have a concentration data value of BLQ for a given time point, the minimum, Q1, and median values will be displayed as "BLQ."
- If more than 75% of the subjects have a concentration data value of BLQ for a given time point, the minimum, Q1, median, and Q3 values will be displayed as "BLQ."
- If all subjects have concentration data values of BLQ for a given time point, all order statistics (minimum, Q1, median, Q3, and maximum) will be displayed as "BLQ."

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

3.8. Analysis Visit Windows

3.8.1. Definition of Study Day

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

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

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

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

3.8.2. Definition of Analysis Visit Windows

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

In general, the baseline value will be the last nonmissing value on or prior to the first dosing date of study drug. Baseline values for liver tests (ALT, AST, and total bilirubin) will be determined by averaging all values obtained between screening and Baseline/Day1. Therefore these baseline values will not be windowed and taken nominally for summary table purposes.

The early termination (ET), follow-up (FU), and ET-FU visits will not be windowed and taken nominally.

Selected safety and efficacy data collected up to and including the last dosing date plus 30 days (or 42 days for imaging data) will be mapped according to the following analysis windows.

The analysis windows for Vital Signs, Weight, Chemistry, Hematology, Coagulation Panel, Lipid Profile, FibroSURE/FibroTest, and Pooled Cohort Score and Risk, and QoL Pruritus Assessment (VAS-itch and 5D-itch) are provided in Table 3-1.

Table 3-1. Analysis Visit Windows for Vital Signs, Weight, Chemistry, Hematology, Coagulation Panel, Lipid Profile, Pooled Cohort Score and Risk, and QoL Pruritus Assessment (VAS-itch and 5D-itch)

Nominal Visit	Nominal Study Day	Lower Limit	Upper Limit
Baseline	1	(none)	1
Week 1	8	2	18
Week 4	29	19	42
Week 8	57	43	70
Week 12	85	71	98
Week 16	113	99	126
Week 20	141	125	154
Week 24	169	155	≥ 169

The analysis windows for FibroSURE/FibroTest, CK-18, FGF19, C4, ELF (and its components), Free Fatty Acid, ApoA1, ApoB, and Bile Acids are provided in Table 3-2.

Table 3-2. Analysis Visit Windows for FibroSURE/FibroTest, CK-18, FGF19, C4, ELF (and its components), Free Fatty Acid, ApoA1, ApoB, and Bile Acids

Nominal Visit	Nominal Study Day	Lower Limit	Upper Limit
Baseline	1	(none)	1
Week 1	8	2	18
Week 4	29	19	56
Week 12	85	57	126
Week 24	169	127	≥ 169

The analysis windows for Insulin and HOMA-IR are provided in Table 3-3

Table 3-3. Analysis Visit Windows for Insulin and HOMA-IR

Nominal Visit	Nominal Study Day	Lower Limit	Upper Limit
Baseline	1	(none)	1
Week 4	29	2	56
Week 12	85	57	126
Week 24	169	127	≥ 169

The analysis windows for QoL (CLDQ, SF-36, and WPAI), Hemoglobin A1c, 12-lead ECG, and FibroScan®, C-Reactive Protein, MRE, and MRI-PDFF are provided in Table 3-4

Table 3-4. Analysis Visit Windows for QoL (CLDQ, SF-36, and WPAI), Hemoglobin A1c, 12-lead ECG, FibroScan®, C-Reactive Protein, MRE, and MRI-PDFF

Nominal Visit	Nominal Study Day	Lower Limit	Upper Limit
Baseline	1	(none)	1
Week 12	85	2	126
Week 24	169	127	≥ 169

The analysis windows for Waist Circumference are provided in Table 3-5.

Table 3-5. Analysis Visit Windows for Waist Circumference

Nominal Visit	Nominal Study Day	Lower Limit	Upper Limit
Baseline	1	(none)	1
Week 24	169	2	≥ 169

- An unscheduled visit prior to the first dosing of study drug will be included in the calculation of the baseline value.
- For subjects who prematurely discontinue from the study, early termination (ET) data will be summarized as a separate visit, labeled as "Early Termination Visit"
- Data collected on a follow-up visit will be summarized as a separate visit, and labeled "Follow-up Visit."

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. If these multiple measurements occur at the same time or the time is not available, the average of these measurements (for continuous data) will be considered the baseline value.

- For postbaseline 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 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. Subject Enrollment and Disposition

A summary of subject enrollment will be provided for each investigator 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. This summary will present the number of subjects screened, the number of subjects randomized, the number of subjects randomized but never treated if not null, and the number of subjects in each of the categories listed below:

- Safety Analysis Set
- Full Analysis Set
- PK Analysis Set
- PPD
- Continuing study drug
- Completed study drug
- Did not complete study drug with reasons for premature discontinuation of study drug
- Continuing study
- Completed study
- Did not complete the study with reasons for premature discontinuation of study

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

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

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

Total duration of exposure to study drug will be defined as last dosing date minus first dosing date plus 1, regardless of any temporary interruptions in study drug administration, and will be expressed in weeks, ie, dividing days by 7, using up to 1 decimal place (eg, 4.5 weeks). If the last study drug dosing date is missing, the latest date among the study drug end date, clinical visit date, laboratory sample collection date, and vital signs assessment date that occurred during the on-treatment period will be used.

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

The total duration of exposure to study drug will be summarized using descriptive statistics and using the number (ie, cumulative counts) and percentage of subjects exposed through the following time periods: 1 day, 1 week, 4 weeks, 8 weeks, 12 weeks, 16 weeks, 20 weeks, and 24 weeks. Summaries will be provided by treatment group for the Safety Analysis Set.

No formal statistical testing is planned.

4.2.2. Adherence to Study Drug

The total number of 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:

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

4.2.2.1. Prescribed Adherence

The level of prescribed adherence to the study drug regimen will be determined by the total amount of study drug administered relative to the total amount of study drug specified by the protocol for a subject who completes treatment in the study.

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

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

Note: If calculated adherence is greater than 100%, the result will be set to 100%.

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

No formal statistical testing is planned.

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

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

5. BASELINE CHARACTERISTICS

5.1. Demographics

Subject demographic variables (ie, age, sex, race, and ethnicity) will be summarized by treatment group and overall using descriptive statistics for age, and using number and percentage of subjects for sex, race, and ethnicity. Age is calculated in years at the date of first study drug administration. The summary of demographic data will be provided for the Safety Analysis Set.

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

5.2. Other Baseline Characteristics

Other baseline characteristics include:

- body weight (kg),
- height (cm),
- body mass index (BMI; in kg/m^2) as a continuous variable and as categories (<18.5 kg/m^2, 18.5 to <25 kg/m^2, 25 to <30 kg/m^2 and ≥ 30 kg/m^2),
- waist circumference (cm)
- diabetes mellitus (absence or presence)
- MRI-PDFF
- MRE
- FibroScan (if available)
- FibroSURE/FibroTest
- ELF test score and its components
- ALP
- ALT
- AST
- direct and total bilirubin
- GGT
- serum creatinine

- fasting homeostasis model assessment of insulin resistance (HOMA-IR)
- fasting glucose
- fasting insulin
- international normalized ratio (INR)
- hemoglobin A1c (HbA1c)
- total cholesterol
- fasting triglycerides
- high density lipoprotein cholesterol (HDL-C)
- calculated fasting low density lipoprotein cholesterol (LDL-C)
- calculated fasting non-HDL-C (total cholesterol - HDL-C)
- calculated fasting very low density lipoprotein cholesterol (VLDL-C)
- fasting total bile acids
- fasting free fatty acid
- C-reactive protein (CRP)
- FGF19
- C4
- systolic blood pressure treated status (treated/not treated)
- smoking status

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

A by-subject listing of the Other Baseline Characteristics will be provided by subject ID number in ascending order.

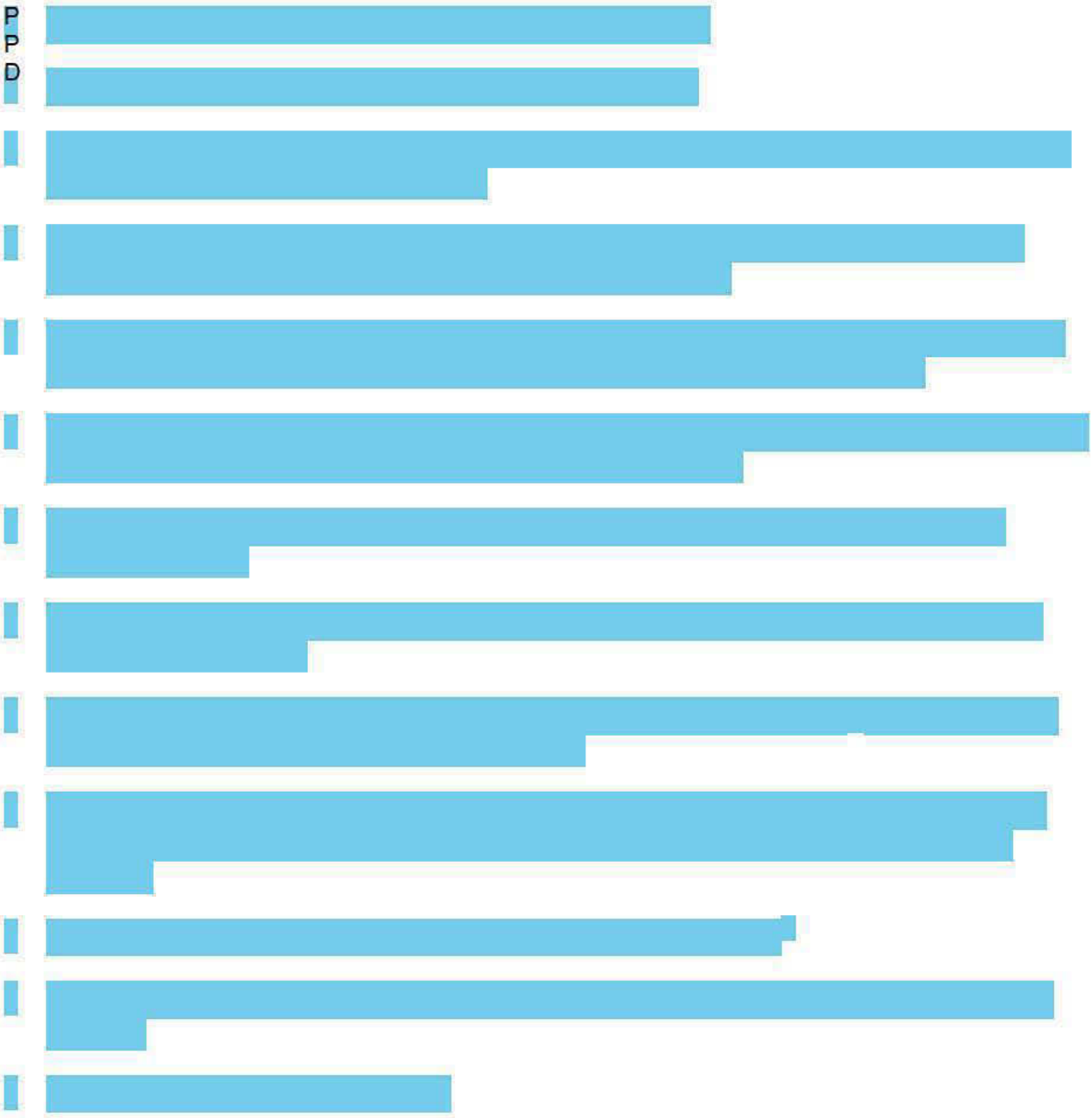
5.3. Medical History

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

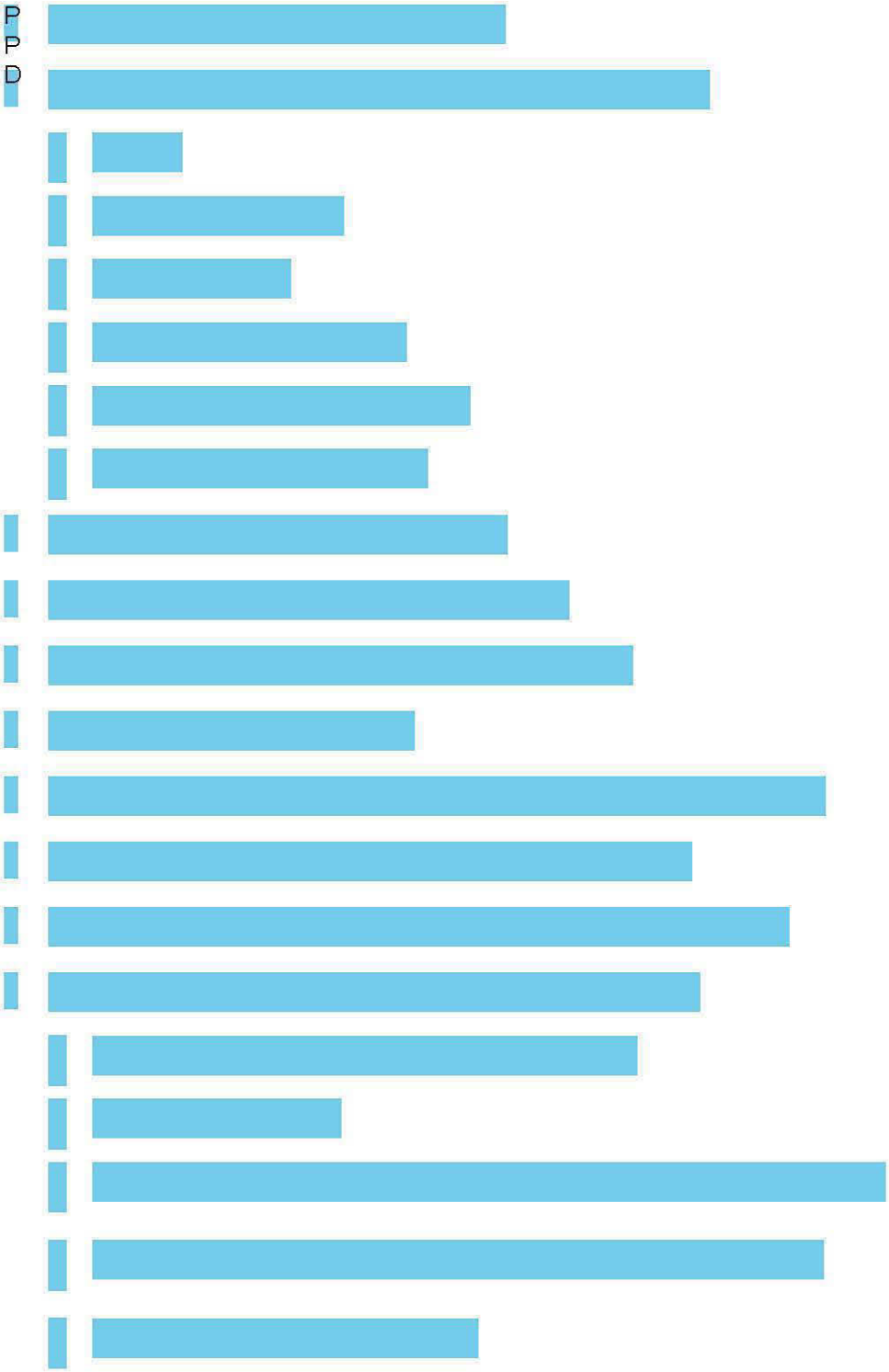
6. EFFICACY ANALYSES

All analyses will be conducted at the Interim Analysis (Week 12) and repeated at the Final Analysis (Week 24). The Interim Analysis will evaluate all changes at Week 12 but will not assess changes at Week 24 even if some data is available. The Final Analysis will evaluate all the changes at both time points, Week 12 and Week 24.

6.1. Exploratory Efficacy Endpoints



P
P
D



6.1.1. Calculation and Remarks for Some Efficacy Endpoints

[redacted]

6.2. Analysis Methods for Exploratory Efficacy Endpoints

6.2.1. Statistical Analysis Models

This study is not designed to evaluate any formal statistical hypotheses. Any statistical analysis

[redacted]

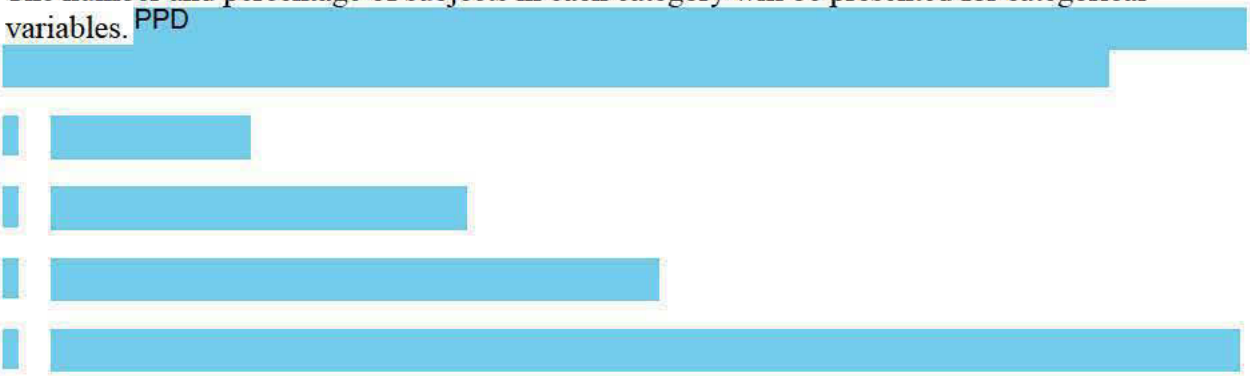
PPD

PPD

PPD

6.2.2. Statistical Analysis Methods

The number and percentage of subjects in each category will be presented for categorical variables. PPD



Change from baseline at a postbaseline visit will be defined as the visit value minus the baseline value. Percent change from baseline will be defined as (the visit value – the baseline value)/the baseline value×100%. The mean, median, Q1, Q3, minimum, and maximum will be displayed to the same reported number of digits, and SD will be reported to the number of digits plus 1.

PPD

PPD

6.2.3. Missing MRI-PDFF Data Handling

For MRI-PDFF data, the first analyzable value (identified as analyzable or marginally analyzable) from multiple-echo (ME) series at each time point will be used. Specifically, the reported mean PDFF by time point will be used. Not analyzable samples will be excluded.

For the Interim Analysis at Week 12 no imputation will be made if a mean ME value is missing.

For the Final Analysis at Week 24 imputations for the mean ME value might be performed if the following condition is met. The 95% CI based on t statistics will be calculated for the mean difference in ME and double-double-echo (DDE) mean series results among all subjects and all time points where ME and DDE are available. If the confidence interval is within [-3%, 3%], then the reported mean DDE values will be used to impute for missing mean ME results.

If a subject has a mean ME result missing at one or more time points and all mean DDE values are available, then the mean DDE values will be used even for the time points at which mean ME was not missing. If imputation of mean ME is needed but at least one of the mean DDE values is missing at another time point, then imputation will only be done for the missing mean ME but no substitution of mean DDE for mean ME will be done at the other time points. See Appendix 5 for a comprehensive description of different scenarios.

6.2.4. Imaging Data Repeat Scan

For MRI-PDFF and MRE data, if a subject has an analyzable repeat scan, then only the repeat scan for that visit will be used for the analysis. For MRE data, if a subject has a re-read result, then the re-read result for that visit will be used for analysis.

6.3. Subgroup Analysis of the Efficacy Endpoints

Subgrouping of subjects based on randomization stratification factors will be explored as follows:

- presence of diabetes mellitus
- absence of diabetes mellitus

Descriptive statistic for the above subgroups will be presented for the baseline values, values at each postbaseline visit, change from baseline, and percent change from baseline by visit for MRE and MRI-PDFF.

For each subgroup, the proportion of subjects with at least 30% reduction in MRI-PDFF and the proportion of subjects with at least 15% reduction in MRE will be reported for each treatment group by using a point estimate and 95% CI of the proportion based on the Clopper-Pearson method. The 95% CI for the difference in proportion between GS-9674 and Placebo will also be provided.

Within each subgroup, the change from baseline of MRI-PDFF (MRE) will be analyzed by using an ANCOVA model, with treatment group, and baseline MRI-PDFF (MRE) as covariates. For change from baseline, LS means and 95% CIs of LS means will be reported for each treatment group. For treatment differences (GS-9674 – Placebo) of changes from baseline of MRI-PDFF (MRE), difference in LS means and 95% CIs will be reported.

Mean (SD) of the observed change from baseline value will be plotted using a line plot by treatment group and visit for subjects from each subgroup.

6.4. Changes From Protocol-Specified Efficacy Analyses

There is no change from protocol specified analysis.

7. SAFETY ANALYSES

7.1. Adverse Events and Deaths

7.1.1. Adverse Event Dictionary

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

7.1.2. Adverse Event Severity

Adverse events are graded by the investigator as Grade 1, 2, 3, 4, or 5 according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03. The severity grade of events for which the investigator did not record severity will be categorized as "missing" for tabular summaries and data listings. The missing category will be listed last in summary presentation.

7.1.3. Relationship of Adverse Events to Study Drug

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

7.1.4. Serious Adverse Events

Serious adverse events (SAEs) will be identified and captured as SAEs if 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
- Any AEs leading to premature discontinuation of study drug.

7.1.5.2. Incomplete Dates

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

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

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

7.1.6. Summaries of Adverse Events and Deaths

Treatment-emergent (TE) AEs will be summarized based on the Safety Analysis Set by treatment group.

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

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

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

Multiple events will be counted only once per subject in each summary. Adverse events will be summarized and listed first in alphabetic order of SOC and HLT within each SOC (if applicable), and then by PT in descending order of frequency in the GS-9674 100 mg group within each SOC. For summaries by severity grade, the most severe grade will be used for those AEs that occurred more than once in an individual subject during the study.

In addition to the above summary tables, TEAEs and TE treatment-related AEs will be summarized by PT only for the following, in descending order of frequency in the GS-9674 100 mg group.

- TE Adverse Events by Preferred Term
- Grade 3 or Higher TEAEs by Preferred Term
- Grade 2 or Higher TEAEs by Preferred Term
- TE treatment-Related AEs by Preferred Term
- Grade 3 or Higher TE treatment-Related AEs by Preferred Term
- Grade 2 or Higher TE treatment-Related AEs by Preferred Term
- All TE SAEs by Preferred Term
- All TE treatment-related SAEs by Preferred Term
- All TEAEs leading to premature discontinuation of study drug by Preferred Term
- All TEAEs leading to premature discontinuation of study by Preferred Term
- All TEAEs leading to temporary interruption of study drug by Preferred Term

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 2 or higher
- SAEs

- Deaths
- All SAEs leading to death (ie, outcome of death)
- AEs leading to premature discontinuation of study drug
- AEs leading to dose modifications or temporary interruption of study drug
- AEs leading to dose reduction of study drug]

7.2. Laboratory Evaluations

Laboratory data collected during the study will be analyzed and summarized using both quantitative and qualitative methods. Summaries of laboratory data will be provided for the Safety Analysis Set and will include data collected up to the last dose of study drug plus 30 days for subjects who have permanently discontinued study drug, or all available data at the time of the database snapshot for subjects who were ongoing at the time of an interim analysis. The analysis will be based on values reported in conventional units. When values are below the LOQ, they will be listed as such, and the closest imputed value will be used for the purpose of calculating summary statistics as specified in Section 3.7. Hemolyzed test results will not be included in the analysis, but they will be listed in by-subject laboratory listings.

A by-subject listing for laboratory test results will be provided by subject ID number and visit in chronological order for hematology, serum chemistry, and urinalysis separately. Values falling outside of the relevant reference range and/or having a severity grade of 1 or higher according to the CTCAE severity grade, Version 4.03, will be flagged in the data listings, as appropriate. See Appendix 6 for details.

No formal statistical testing is planned.

7.2.1. Summaries of Numeric Laboratory Results

Descriptive statistics will be provided by treatment group for each laboratory test listed below:

- Chemistry Panel: albumin, fasting glucose, serum creatinine
- Fasting insulin
- Coagulation Panel: INR
- Hematology: white blood cell (WBC), neutrophils, lymphocytes, hemoglobin, platelets

For each laboratory test specified above, the descriptive statistics will be provided as follows:

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

Change from baseline to a postbaseline visit will be defined as the postbaseline 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 these laboratory tests 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 to assign toxicity grades (0 to 4) to laboratory results for analysis. Grade 0 includes all values that do not meet the criteria for an abnormality of at least Grade 1. For laboratory tests with criteria for both increased and decreased levels, analyses for each direction (ie, increased, decreased) will be presented separately.

7.2.2.1. Treatment-Emergent Laboratory Abnormalities

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

7.2.2.2. Treatment-Emergent Marked Laboratory Abnormalities

Treatment-emergent marked laboratory abnormalities are defined as values that increase from baseline by at least 3 toxicity grades at any postbaseline time point, up to and including the date of the last dose of study drug plus 30 days for subjects who permanently discontinued study drug or the last available date in the database snapshot for subjects who were still on treatment at the time of an interim analysis. If the relevant baseline laboratory value is missing, any Grade 3 or 4 values observed within the timeframe specified above will be considered treatment-emergent marked abnormalities.

7.2.2.3. Summaries of Laboratory Abnormalities

Laboratory data that are categorical will be summarized using the number and percentage of subjects in the study with the given response at baseline and each scheduled postbaseline visit.

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

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

For all summaries of laboratory abnormalities, the denominator is the number of subjects with nonmissing postbaseline values up to 30 days after last dosing date 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 for the laboratory test of interest.

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 laboratory test of interest, with all applicable severity grades and 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 by groups of subjects according to their baseline ALT/AST level, respectively:

- Normal
- Elevated (≥ upper limit of normal [ULN])

For subjects with normal baseline ALT and AST

- Subjects meeting criteria for liver-related events:
    - ALT or AST > 3 × ULN at any time
    - Total bilirubin > 2 × ULN
    - ALP > 3 × ULN
    - INR >1.5 (except for subjects on anticoagulant therapy)

- Subjects meeting criteria for drug withheld
    - ALT or AST > 5 × baseline
    - ALT or AST >10 × ULN
    - ALT or AST >3 × baseline and total bilirubin > 2 × ULN
    - ALT or AST >3 × baseline and total bilirubin > 1.5 × baseline
    - ALT or AST >3 × baseline and INR >1.5 (except for subjects on anticoagulant therapy)
    - ALT or AST > baseline, total bilirubin > 2 × ULN, and INR >1.5 (except for subjects on anticoagulant therapy)
    - ALT or AST > baseline, total bilirubin > 1.5 × baseline, and INR >1.5 (except for subjects on anticoagulant therapy)

For subjects with ALT or AST ≥ ULN at study start:

- Subjects meeting criteria for liver-related events:
    - ALT or AST > 2 × baseline at any time
    - Total bilirubin > 2 × ULN
    - ALP > 3 × ULN
    - INR >1.5 (except for subjects on anticoagulant therapy)
- Subjects meeting criteria for drug withheld
    - ALT or AST > 5 × baseline
    - ALT or AST >10 × ULN
    - ALT or AST >3 × baseline and total bilirubin > 2 × ULN
    - ALT or AST >3 × baseline and total bilirubin > 1.5 × baseline
    - ALT or AST >3 × baseline and INR >1.5 (except for subjects on anticoagulant therapy)
    - ALT or AST > baseline, total bilirubin > 2 × ULN, and INR >1.5 (except for subjects on anticoagulant therapy)
    - ALT or AST > baseline, 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. For individual laboratory tests, subjects will be counted once based on the most severe postbaseline values. For the composite endpoints of ALT (AST), total bilirubin, and INR, subjects will be counted once when the criteria are met at the same postbaseline visit date. The denominator is the number of subjects in the Safety Analysis Set who have nonmissing postbaseline values of all relevant tests at the same postbaseline visit date. A listing of subjects who met at least 1 of the above criteria will be provided.

7.3. Body Weight, Height, and Vital Signs

Descriptive statistics will be provided by treatment group for body weight, height, BMI, waist circumference, and vital signs (systolic and diastolic blood pressures [mmHg], pulse [beats/min], respiration [breaths/min], and body temperature [°C]) as follows:

- Baseline value
- Values at each postbaseline visit
- Change from baseline at each postbaseline visit
- Percent change from baseline (for weight and waist circumference only)

Change from baseline to a postbaseline visit will be defined as the postbaseline value minus the baseline value. Percent change from baseline will be defined as the change from baseline divided by the baseline value times 100 and displayed as percent (%).

Median (Q1, Q3) of the observed change from baseline values for body weight and waist circumference will be plotted by treatment group and visit.

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

A by-subject listing of vital signs will be provided by subject ID number and visit in chronological order. Body weight, height, and BMI will be provided separately.

7.4. Prior and Concomitant Medications

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

7.4.1. Prior Medications

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

Prior medications will be summarized by Anatomical Therapeutic Chemical (ATC) drug class Level 4 and preferred name using the number and percentage of subjects for each treatment group and overall. A subject reporting the same medication more than once will be counted only

once when calculating the number and percentage of subjects who received that medication. The summary will be ordered alphabetically by ATC medical class and then by preferred term in order of descending overall frequency within each ATC medical class. For drugs with the same frequency, sorting will be done alphabetically.

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

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

7.4.2. Concomitant Medications

Concomitant medications are defined as medications taken while a subject took study drug. Use of concomitant medications will be summarized by Anatomical Therapeutic Chemical (ATC) drug class Level 4 and 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 alphabetically by ATC medical class and then by preferred term in descending overall frequency within each ATC medical class. For drugs with the same frequency, sorting will be done alphabetically.

For the purposes of analysis, any medications with a start date prior to or on the first dosing date of study drug and continued to be taken after the first dosing date, or started after the first dosing date but prior to or on the last dosing date of study drug will be considered concomitant medications. Medications started and stopped on the same day as the first dosing date or the last dosing date of study drug will also be considered concomitant. Medications with a stop date prior to the date of first dosing date of study drug or a start date after the last dosing date of study drug will be excluded from the concomitant medication summary. If a partial stop date is entered, any medication with the month and year (if day is missing) or year (if day and month are missing) prior to the date of first study drug administration will be excluded from the concomitant medication summary. If a partial start date is entered, any medication with the month and year (if day is missing) or year (if day and month are missing) after the study drug stop date will be excluded from the concomitant medication summary. Medications with completely missing start and stop dates will be included in the concomitant medication summary, unless otherwise specified. Summaries will be based on the Safety Analysis Set. No formal statistical testing is planned.

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

7.5. Electrocardiogram Results

A shift table of the investigators' assessment of ECG results at time of analysis 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

A data listing will be provided for subjects experiencing pregnancy during the study.

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 PK blood sample will be collected at any time during each On-Treatment Visit for all subjects.

PPD

8.2. PK Analyses Related to Intensive PK Sampling

PPD

8.2.1. Estimation of PK Parameters

Pharmacokinetic 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.

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

The analytes and parameters presented in Table 8-1 will be used to evaluate the PK objectives of the study. The PK parameters to be estimated are listed in Table 8-1. The PK parameters to be estimated in this study are listed and defined in the PK Abbreviations section.

Table 8-1. PK Parameters for Each Analyte

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

Individual subject concentration data and individual subject PK parameters for GS-9674 and GS-716070 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.

PPD

Individual and mean postdose concentration values that are ≤ LLOQ will not be displayed in the figures and remaining points connected.

PPD

The following listings will be provided for all PK samples collected in this study:

- 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 times, sample age, and sample concentration by analyte.

9. REFERENCES

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

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Sbidian E, Battistella M, Legoff J, Lafaurie M, Bezier M, Agbalika F, et al. Recalcitrant pseudotumoral anogenital herpes simplex virus type 2 in HIV-infected patients: evidence for predominant B-lymphoplasmocytic infiltration and immunomodulators as effective therapeutic strategy. Clin Infect Dis 2013;57 (11):1648-55.

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 for GS-US-402-1852

	Screening[b]	Treatment								Follow-Up	
	Week -6 to Day 0[a]	Baseline /Day 1	Week 1 ± 3 days	Week 4 ± 3 days	Week 8 ± 3 days	Week 12 ± 7 days	Week 16 ± 3 days	Week 20 ± 3 days	Week 24/ET[c] ± 7 days	Follow-Up[c] ± 5 days	Unscheduled Visit[z]
Subject Fasting[d]	X	X	X	X	X	X	X	X	X	X	X
Written Informed Consent[e]	X										
Review Inclusion/Exclusion Criteria	X	X									
Medical History	X										
QoL: General Assessments (CLDQ, SF-36, and WPAI)[f]		X				X			X		
QoL: Pruritus Assessments (VAS-itch and 5D-itch)[f]		X	X	X	X	X	X	X	X		
Complete Physical Examination	X										
Symptom Driven Physical Examination[g]		X	X	X	X	X	X	X	X	X	X
Vital Signs[h]	X	X	X	X	X	X	X	X	X	X	
Weight[i]	X	X[j]	X	X	X	X	X	X	X[j]	X	X
Height	X										

	Screening[b]	Treatment								Follow-Up	
	Week -6 to Day 0[a]	**Baseline /Day 1**	**Week 1 ± 3 days**	**Week 4 ± 3 days**	**Week 8 ± 3 days**	**Week 12 ± 7 days**	**Week 16 ± 3 days**	**Week 20 ± 3 days**	**Week 24/ET[c] ± 7 days**	**Follow-Up[c] ± 5 days**	**Unscheduled Visit[z]**
Chemistry[k]	X	X	X	X	X	X	X	X	X	X	X
Hematology[l]	X	X	X	X	X	X	X	X	X	X	X
Coagulation Panel[m]	X	X	X	X	X	X	X	X	X	X	
Lipid Profile		X	X	X	X	X	X	X	X		
Hemoglobin A1c	X	X				X			X		
Blood for Biomarkers[n]	X	X	X	X		X			X		
Single PK and PD Sampling		X[o]	X	X	X	X	X	X	X		
HIV-1, HBV and HCV Serology	X										
Pregnancy Test[p]	X	X		X	X	X	X	X	X	X	
Serum FSH[q]	X										
Genomic Sample[r]		X									
12-lead ECG	X	X				X			X		
Ultrasound[s]	X[r]										
FibroScan®[t]		X				X			X		
MRE[u]	X					X			X		
MRI-PDFF[u]	X					X			X		
Urine Drug Screen[v]	X										
Urine Collection for (Biomarker)		X	X	X		X			X		

	Screening[b]	Treatment								Follow-Up	
	Week -6 to Day 0[a]	Baseline /Day 1	Week 1 ± 3 days	Week 4 ± 3 days	Week 8 ± 3 days	Week 12 ± 7 days	Week 16 ± 3 days	Week 20 ± 3 days	Week 24/ET[c] ± 7 days	Follow-Up[c] ± 5 days	Unscheduled Visit[z]
Stool Collection for (Biomarker)		X							X		
PPD											
Review of Study Drug Dosing Compliance (Pill Count)			X	X	X	X	X	X	X		X
Dispense GS-9674 and PTM GS-9674[x]		X		X	X	X	X	X			
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X
Take GS-9674/ PTM GS-9674 Tablets[y]		X – Daily (Baseline/ Day 1 to Week 24)									

a. The screening 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 with prior approval of the Medical Monitor.
b. Subjects who failed screening may be re-screened under certain circumstances and at the discretion of the investigator. See Section 6.2 and the Study Reference Binder for re-screening guidelines
c. Subjects discontinuing the study at any time for any reason (Early Termination – ET) should complete the procedures listed for the Week 24/ET Visit AND the Follow-Up visit.
d. Subjects must be in a fasted state for at least 8 hours prior to blood collection.
e. Obtain written informed consent before initiation of any screening procedure.
f. It is recommended that QoL assessments 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 assessment administration.
g. The focus of a symptom driven physical examination will be determined by the investigator based on subject complaint.
h. Vital signs include blood pressure, heart rate, respiration rate, and body temperature.
i. Refer to the Study Reference Binder for specific instructions on how weight should be measured.
j. During the Baseline/Day 1 and Week 24 visits, measurements of waist circumference should be performed. Refer to the Study Reference Binder for specific instructions on how these measurements are to be done.
k. Blood chemistry will include: alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin, alkaline phosphatase, bicarbonate, blood urea nitrogen (BUN), calcium, chloride, creatinine, glucose, lactate dehydrogenase (LDH), magnesium, phosphorus, potassium, sodium, total and direct bilirubin, total protein, uric acid, gamma-glutamyl transferase (GGT). Also includes C-Peptide and Insulin for the Baseline/Day 1, Week 4, 12, and 24 visits.

l. Hematology will include: complete blood cell count with differential (red blood cells, white blood cells, platelets, and hematocrit).
m. Coagulation Panel includes: PT, PTT, and INR.
n. PPD
o. Only PD sampling at Baseline/Day 1.
p. Females of childbearing potential only (see Protocol). Serum pregnancy test at Screening and Urine pregnancy test at all other visits, except Week 1.
q. Only required for some female subjects – see Protocol.
r. PPD .
s. Ultrasound may be performed if necessary to confirm NAFLD.
t. 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.
u. Subjects should be in fasted state for MRE/MRI-PDFF exams. Refer to the Study Reference Binder for further details. Subject must have confirmed NAFLD (from prior imaging) OR a historical biopsy consistent with NASH and non-cirrhotic fibrosis before MRE/MRI-PDFF exams are done. If MRE/MRI-PDFF were performed within 6 months of re-screening, MRE and MRI-PDFF do not need to be repeated. If prior imaging was performed greater than 6 months prior to re-screening, MRE and MRI-PDFF must be repeated. A historical MRE and MRI-PDFF within 6 months of screening in another Gilead study (i.e. GS-US-384-1497, GS-US-426-3989) may be used to determine eligibility for this study. All other screening procedures must be repeated and meet eligibility criteria.
v. Drug screen for amphetamines, cocaine, and opiates (ie, heroin, morphine).
w. PPD .
x. Study drug will be assigned via the IWRS system every 4 weeks from Baseline/Day 1 through Week 20.
y. Subjects will self-administer the study drug at the investigative site at the conclusion of the Baseline/Day 1 and Week 24 visits.

Appendix 2. Pooled Cohort Score and Risk Calculation

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	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	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 subject, 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 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)** = 1 - Baseline Survival ^ exp (Individual Sum- Population Mean)			

* ASCVD = atherosclerotic cardiovascular disease; BP = blood pressure (mm Hg); 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 at the visits in BD Phase, and prior to the visit date for the OLE Phase, if started during the OLE Phase. Round Pooled Cohort Risk Score and estimated risk of ASCVD events to 0.001.

Appendix 3. Health Related QoL Score Calculation

- SF-36 (Short Form (36) Health Survey)

Scoring of the SF-36 scales will be performed as described in Chapter 6 of the SF-36 Health Survey Manual and Interpretation Guide, Version 2. Summary will be done for 8 domains of the SF-36 (physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health), and for the physical component score and mental component summary.

- CLDQ (Chronic Liver Disease Questionnaire)

CLDQ scores are calculated using subject responses to 29 questions in the questionnaire. If Ri is the score for the subject's response to the item i, for i=1, 2, …., 29 then the 6 domain scores are calculated as follows:

- Abdominal (AB) = Mean of {R1, R5, R17}
- Fatigue (FA) = Mean of {R2, R4, R8, R11, R13}
- Systemic (SY) = Mean of {R3, R6, R21, R23, R27}
- Activity (AC) = Mean of {R7, R9, R14}
- Emotion (EM) = Mean of {R10, R12, R15, R16, R19, R20, R24, R26}
- Worry (WO) = Mean of {R18, R22, R25, R28, R29}

Here "Mean" is the average of nonmissing items (SAS mean function). Each score is calculated only if at least half of corresponding items are not missing. Otherwise, the score will be missing.

Overall CLDQ score is calculated by taking the mean of 6 domain scores {AB, FA, SY, AC, EM, WO}. Overall CLDQ score will be summarized.

- WPAI (Work Productivity and Activity Impairment): SHP

The response to Question 1 of this questionnaire provides the binary endpoint whether or not the subject had been in a paid employment during the week prior to assessment.

If the subject had been in a paid employment (Response to Q1 is "Yes") at the visit when questionnaire was given, then following three scores are derived:

Percent work time missed (Absenteeism) = $100 \times Q2 / (Q2 + Q4)$

Percent impairment while working (Presenteeism) = $100 \times Q5 / 10$

Percent overall work productivity loss =

$$100 \times \left[\frac{Q2}{(Q2+Q4)} + \left(1 - \frac{Q2}{Q2+Q4} \right) \times \frac{Q5}{10} \right]$$

Question 6 is applicable to all subjects:

Percent activity impairment = 100 × Q6 / 10.

Percent overall work productivity loss and percent activity impairment will be summarized.

Appendix 4. 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

Note: 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**

  HOMA-IR = fasting Glucose (mg/dL) x fasting Insulin (uIU/mL) / 405.

  Keep 2 decimal places. If fasting plasma glucose is missing but fasting serum glucose is present, use fasting serum glucose. The lab parameters need to be measured from the same blood draw.

- **Serum lipid profiles**

  - Calculated Non-HDL cholesterol (= total cholesterol minus HDL-cholesterol)
  - Calculated Very Low Density Lipoprotein (VLDL) (= triglycerides divided by 5 if in mg/dL, or triglycerides divided by 2.2 if in mmol/L. If the triglyceride level is greater than 400 mg/dl (4.5 mmol/L), VLDL will not be calculated.)
  - Calculated LDL = Non-HDL - VLDL

  Note: The lab parameters need to be measured from the same blood draw.

- **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) 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 and then summed together to obtain a total 5D-Itch score. 5D-Itch scores can potentially range between 5 (no pruritus) and 25 (most severe pruritus). {Elman et al 2010}

Appendix 5. Imputation of mean ME values

No imputation will be conducted before the following condition is met. The 95% CI based on t statistics will be calculated for the mean difference in ME and DDE mean series results among all subjects and all time points where ME and DDE are available. If the confidence interval is within [-3%, 3%], then the reported mean DDE values will be used to impute for missing mean ME results.

Scenario	Time points	Mean ME	Mean DDE	Used for analysis
1	Screening	Available	N/A	ME
	Week 12	Available	N/A	ME
	Week24	Available	N/A	ME
2	Screening	Available	Available	DDE
	Week 12	Missing	Available	DDE
	Week24	Available	Available	DDE
3	Screening	Available	Missing	ME
	Week 12	Missing	Available	DDE
	Week24	Available	Available	ME

Appendix 6. CTCAE Grade for Laboratory Parameters

CTCAE v4.03	CTCAE Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Anemia	Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated	Life-threatening consequences; urgent intervention indicated	Death
Hypoalbuminemia	<LLN - 3 g/dL; <LLN - 30 g/L	<3 - 2 g/dL; <30 - 20 g/L	<2 g/dL; <20 g/L	Life-threatening consequences; urgent intervention indicated	Death
Alkaline phosphatase increased	>ULN – 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN	-
Alanine aminotransferase (ALT) increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN	-
Activated partial thromboplastin time (APTT) prolonged	>ULN - 1.5 x ULN	>1.5 - 2.5 x ULN	>2.5 x ULN; hemorrhage	-	-
Aspartate aminotransferase (AST) increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN	-
Blood bilirubin increased	>ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 - 10.0 x ULN	>10.0 x ULN	-
Hypercalcemia	Corrected serum calcium of >ULN - 11.5 mg/dL; >ULN - 2.9mmol/L; Ionized calcium >ULN- 1.5 mmol/L	Corrected serum calcium of>11.5 - 12.5 mg/dL; >2.9 - 3.1 mmol/L; Ionized calcium >1.5 -1.6 mmol/L; symptomatic	Corrected serum calcium of >12.5 - 13.5 mg/dL; >3.1 - 3.4 mmol/L; Ionized calcium >1.6 - 1.8 mmol/L; hospitalization indicated	Corrected serum calcium of >13.5 mg/dL; >3.4 mmol/L; Ionized calcium >1.8 mmol/L; life-threatening consequences	Death

CTCAE v4.03	CTCAE Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Hypocalcemia	Corrected serum calcium of <LLN - 8.0 mg/dL; <LLN - 2.0 mmol/L; Ionized calcium <LLN - 1.0 mmol/L	Corrected serum calcium of <8.0 - 7.0 mg/dL; <2.0 - 1.75 mmol/L; Ionized calcium <1.0 - 0.9 mmol/L; symptomatic	Corrected serum calcium of <7.0 - 6.0 mg/dL; <1.75 - 1.5 mmol/L; Ionized calcium <0.9 - 0.8 mmol/L; hospitalization indicated	Corrected serum calcium of <6.0 mg/dL; <1.5 mmol/L; Ionized calcium <0.8 mmol/L; life-threatening consequences	Death
Chronic kidney disease	eGFR (estimated Glomerular Filtration Rate) or CrCl (creatinine clearance) <LLN – 60 ml/min/1.73 m2 or proteinuria 2+ present; urine protein/creatinine >0.5	eGFR or CrCl 59 – 30 ml/min/1.73 m2	eGFR or CrCl 29 – 15 ml/min/1.73 m2	eGFR or CrCl <15 ml/min/1.73 m2; dialysis or renal transplant indicated	Death
Creatinine increased	>1 - 1.5 x baseline; >ULN - 1.5 x ULN	>1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	>3.0 baseline; >3.0 - 6.0 x ULN	>6.0 x ULN	-
Gamma-glutamyl transferase (GGT) increased	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN	-
Hyperglycemia	Fasting glucose value >ULN - 160 mg/dL; Fasting glucose value >ULN - 8.9 mmol/L	Fasting glucose value >160 - 250 mg/dL; Fasting glucose value >8.9 - 13.9 mmol/L	>250 - 500 mg/dL; >13.9 - 27.8 mmol/L; hospitalization indicated	>500 mg/dL; >27.8 mmol/L; lifethreatening consequences	Death
Hypoglycemia	<LLN - 55 mg/dL; <LLN - 3.0 mmol/L	<55 - 40 mg/dL; <3.0 - 2.2 mmol/L	<40 - 30 mg/dL; <2.2 - 1.7 mmol/L	<30 mg/dL; <1.7 mmol/L; lifethreatening consequences; seizures	Death
Hemoglobin increased	Increase in >0 - 2 gm/dL above ULN or above baseline if baseline is above ULN	Increase in >2 - 4 gm/dL above ULN or above baseline if baseline is above ULN	Increase in >4 gm/dL above ULN or above baseline if baseline is above ULN	-	-
International normalized ratio (INR) increased	>1 - 1.5 x ULN; >1 - 1.5 times above baseline if on anticoagulation	>1.5 - 2.5 x ULN; >1.5 - 2.5 times above baseline if on anticoagulation	>2.5 x ULN; >2.5 times above baseline if on anticoagulation	-	-

CTCAE v4.03	CTCAE Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Hyperkalemia	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L	>6.0 - 7.0 mmol/L; hospitalization indicated	>7.0 mmol/L; life-threatening consequences	Death
Hypokalemia	<LLN - 3.0 mmol/L	<LLN - 3.0 mmol/L; symptomatic; intervention Indicated	<3.0 - 2.5 mmol/L; hospitalization indicated	<2.5 mmol/L; life-threatening consequences	Death
Lymphocyte count decreased	<LLN - 800/mm3; <LLN - 0.8 x 10e9 /L	<800 - 500/mm3; <0.8 - 0.5 x 10e9 /L	<500 - 200/mm3; <0.5 - 0.2 x 10e9 /L	<200/mm3; <0.2 x 10e9 /L	-
Lymphocyte count increased	-	>4000/mm3 - 20,000/mm3	>20,000/mm3	-	-
Hypermagnesemia	>ULN - 3.0 mg/dL; >ULN - 1.23 mmol/L	-	>3.0 - 8.0 mg/dL; >1.23 - 3.30 mmol/L	>8.0 mg/dL; >3.30 mmol/L; lifethreatening consequences	Death
Hypomagnesemia	<LLN - 1.2 mg/dL; <LLN - 0.5 mmol/L	<1.2 - 0.9 mg/dL; <0.5 - 0.4 mmol/L	<0.9 - 0.7 mg/dL; <0.4 - 0.3 mmol/L	<0.7 mg/dL; <0.3 mmol/L; lifethreatening consequences	Death
Neutrophil count decreased	<LLN - 1500/mm3; <LLN - 1.5 x 10e9 /L	<1500 - 1000/mm3; <1.5 - 1.0 x 10e9 /L	<1000 - 500/mm3; <1.0 - 0.5 x 10e9 /L	<500/mm3; <0.5 x 10e9 /L	-
Hypophosphatemia	<LLN - 2.5 mg/dL; <LLN - 0.8 mmol/L	<2.5 - 2.0 mg/dL; <0.8 - 0.6 mmol/L	<2.0 - 1.0 mg/dL; <0.6 - 0.3 mmol/L	<1.0 mg/dL; <0.3 mmol/L; lifethreatening consequences	Death
Platelet count decreased	<LLN - 75,000/mm3; <LLN - 75.0 x 10e9 /L	<75,000 - 50,000/mm3; <75.0 - 50.0 x 10e9 /L	<50,000 - 25,000/mm3; <50.0 - 25.0 x 10e9 /L	<25,000/mm3; <25.0 x 10e9 /L	-
Hypernatremia	>ULN - 150 mmol/L	>150 - 155 mmol/L	>155 - 160 mmol/L; hospitalization indicated	>160 mmol/L; life-threatening consequences	Death
Hyponatremia	<LLN - 130 mmol/L	-	<130 - 120 mmol/L	<120 mmol/L; life-threatening consequences	Death
Hyperuricemia	>ULN - 10 mg/dL (0.59 mmol/L) without physiologic consequences	-	>ULN - 10 mg/dL (0.59 mmol/L) with physiologic consequences	>10 mg/dL; >0.59 mmol/L; lifethreatening consequences	Death
White blood cell (WBC) decreased	<LLN - 3000/mm3; <LLN - 3.0 x 10e9 /L	<3000 - 2000/mm3; <3.0 - 2.0 x 10e9 /L	<2000 - 1000/mm3; <2.0 - 1.0 x 10e9 /L	<1000/mm3; <1.0 x 10e9 /L	-

CTCAE v4.03	CTCAE Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Hypertriglyceridemia	150 mg/dL - 300 mg/dL; 1.71 mmol/L - 3.42 mmol/L	>300 mg/dL - 500 mg/dL; >3.42 mmol/L - 5.7 mmol/L	>500 mg/dL - 1000 mg/dL; >5.7 mmol/L - 11.4 mmol/L	>1000 mg/dL; >11.4 mmol/L; life-threatening consequences	Death
Cholesterol high	>ULN - 300 mg/dL; >ULN - 7.75 mmol/L	>300 - 400 mg/dL; >7.75 - 10.34 mmol/L	>400 - 500 mg/dL; >10.34 - 12.92 mmol/L	>500 mg/dL; >12.92 mmol/L	-