STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 1 Open-Label, Parallel-Group, Adaptive, Single-Dose Study to Evaluate the Pharmacokinetics and Pharmacodynamics of GS-9674 in Subjects with Normal and Impaired Hepatic Function
Study Phase:	1
Name of Test Drug:	GS-9674
Study Number:	GS-US-402-3885
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CONFIDENTIAL AND PROPRIETARY INFORMATION

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%CV	% coefficient of variation
AE	adverse event
ALT	alanine aminotransferase
ANOVA	analysis of variance
AST	aspartate aminotransferase
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
CLcr	creatinine clearance
CPT	Child-Pugh-Turcotte classification system for hepatic impairment
CRF	case report form
CSR	clinical study report
DMC	data monitoring committee
ECG	electrocardiogram
eCRF	electronic case report form
ET	early termination
FGF19	fibroblast growth factor 19
FU	follow-up
FSH	follicle-stimulating hormone
Gilead	Gilead Sciences
GLSM	geometric least-squares mean
Hb	hemoglobin
HLGT	high-level group term
HLT	high-level term
ICH	International Conference on Harmonization (of Technical Requirements for Registration of Pharmaceuticals for Human Use)
ID	identification
LLOQ	lower limit of quantitation
LLT	lower-level term
LOQ	limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
PD	pharmacodynamic
PK	pharmacokinetics
PT	preferred term
PTM	placebo-to-match
Q1, Q3	first quartile, third quartile
SAE	serious adverse event

SAP	statistical analysis plan
SD	standard deviation
SE	standard error
SI	International System of Units (Systeme International d'Unites)
SOC	system organ class
TE	treatment-emergent
TEAE	treatment-emergent adverse event
TFLs	tables, figures, and listings
TOST	two one-sided tests
ULN	upper limit of normal
WHO	World Health Organization

PHARMACOKINETIC AND PHARMACODYNAMIC ABBREVIATIONS

λ_z	terminal elimination rate constant, estimated by linear regression of the terminal elimination phase of the log plasma/serum concentration of drug versus time curve of the drug
$\%AUC_{exp}$	percentage of AUC extrapolated between AUC_{last} and AUC_{inf}
$\%Dose_{excreted}$	percentage of given dose excreted in the urine as unchanged drug calculated as $100(A_e/dose)$
A_e	amount of unchanged drug excreted in urine calculated either over a specific interval ($A_{e(interval)}$) or cumulatively over all collection intervals, calculated as (concentration of unchanged drug in urine) × (volume of urine collected)
AUC	area under the plasma/serum concentration versus time curve
AUC_{last}	area under the plasma/serum concentration versus time curve from time zero to the last quantifiable concentration
AUC_{inf}	area under the plasma/serum concentration versus time curve extrapolated to infinite time, calculated as $AUC_{last} + (C_{last}/\lambda_z)$
AUC_{x-xx}	partial area under the plasma/serum concentration versus time curve from time "x" to time "xx"
CL	clearance
CL/F	apparent oral clearance after administration of the drug: $CL/F = Dose/AUC_{inf}$, where "Dose" is the dose of the drug
C_{last}	last observed quantifiable plasma/serum concentration of the drug
CL_p	plasma clearance
C_{max}	maximum observed plasma/serum concentration of drug
C_{min}	minimum observed plasma/serum concentration of drug
F	estimated oral bioavailability of the drug (%), calculated as $100(AUC_{oral} \times Dose_{iv})/(AUC_{iv} \times Dose_{oral})$
f_u	unbound fraction
$t_{½}$	estimate of the terminal elimination half-life of the drug in plasma/serum, 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}
V_d	volume of distribution
V_z	volume of distribution of the drug after intravenous administration
V_z/F	apparent volume of distribution of the drug

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-402-3885. This SAP is based on the study protocol amendment 2 dated 23 March 2018 and the electronic case report form (eCRF). The SAP will be finalized prior to database finalization. Any changes made after 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 single-dose pharmacokinetics (PK) of GS-9674 in subjects with impaired hepatic function relative to matched, healthy controls with normal hepatic function

The secondary objectives of this study are as follows:

- To evaluate the safety and tolerability of GS-9674 single dose administration in subjects with normal hepatic function, or mild, moderate, and severe hepatic impairment
- To evaluate Farnesoid X Receptor (FXR) activation by GS-9674 as measured by pharmacodynamic (PD) markers in subjects with normal hepatic function, or mild, moderate and severe hepatic impairment

1.2. Study Endpoints

The primary endpoints are single dose plasma PK parameters of GS-9674 AUC_{last}, AUC_{inf}, and C_{max}.

Secondary endpoints are the incidences of adverse events (AE) and laboratory abnormalities, physical examinations, vital signs, electrocardiogram (ECG), and PD parameters.

1.3. Study Design

This is a Phase 1, open-label, single-dose, parallel-group, staggered-cohort, PK study of GS-9674 in subjects with mildly, moderately and severely impaired hepatic function and matched normal (control) groups.

Subjects with hepatic impairment in each cohort will be enrolled based upon the Child-Pugh-Turcotte (CPT) classification system for hepatic impairment:

- Cohort 1: mild hepatic impairment (CPT Class A; score of 5-6) and matched control
- Cohort 2 : moderate hepatic impairment (CPT Class B; score of 7-9) and matched control
- Cohort 3: severe hepatic impairment (CPT Class C; score of 10-15) and matched control

The matched control group will consist of matched healthy subjects with normal hepatic function.

Up to approximately 60 (20 per cohort, 10 per group) male and non-pregnant/non-lactating female subjects aged ≥ 18 years with impaired and normal hepatic function will be enrolled to ensure completion of 48 (16 per cohort, 8 per group) evaluable subjects. Each subject in the control group will be matched for age (± 10 years), gender, race, and body mass index (± 15% $18 \leq BMI \leq 36$ kg/m^2) with a subject in the hepatic impairment group. A subject with normal hepatic function may serve as a matched control across cohorts evaluating the same GS-9674 dose. Subjects with hepatic impairment must have the respective CPT Classification at Screening without evidence of worsening clinical and/or laboratory signs of hepatic impairment within 2 months prior or within the screening period.

Following screening procedures and Day -2 admission assessments, eligible subjects will be enrolled in one of three sequential cohorts. Subjects will undergo intensive sampling over 24 hours on Day -1 after administration of placebo-to-match (PTM) for baseline PD markers. On Day 1 subjects will receive a single dose of GS-9674 30 mg (3 x 10 mg tablet) orally for Cohorts 1 and 2, or 10 mg (1 x 10mg tablet) for Cohort 3. Study Treatments will be administered in the fed state. Subjects will be confined to the clinic for the duration of the study until discharge on Day 5. Subjects will be required to return for a Follow-up (FU) visit 10-14 days after study drug dosing.

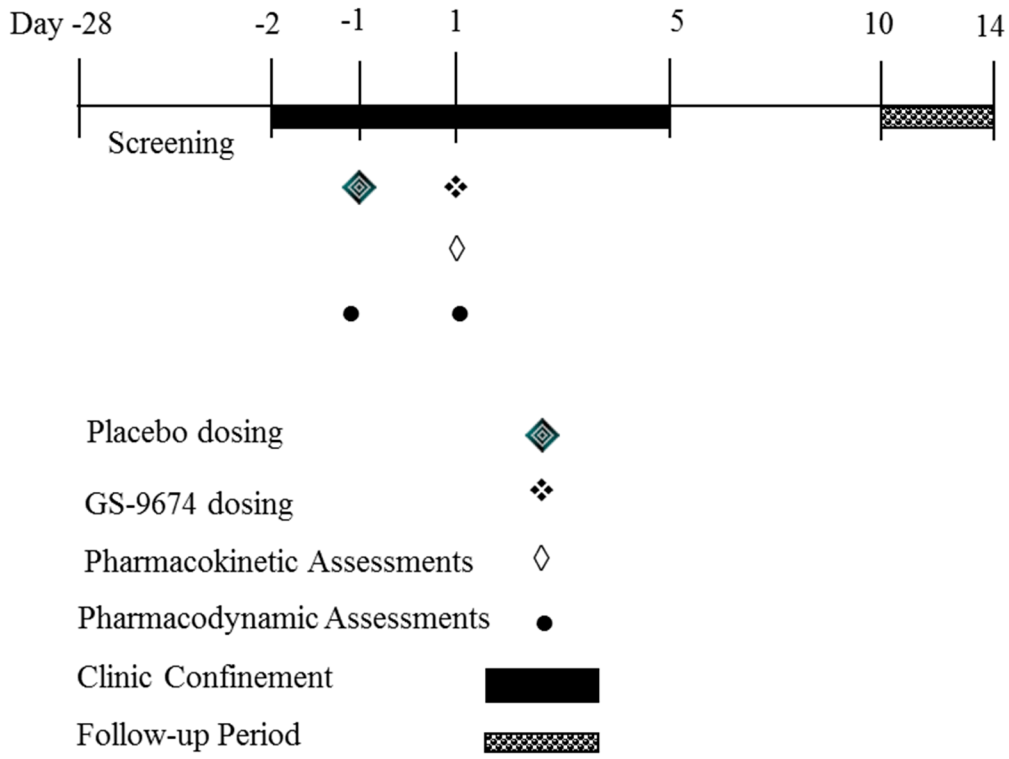
In general, dosing in subjects with normal hepatic function will begin after a matched subject with hepatic impairment has completed PK assessments.

Cohorts 1 through 3 will be dosed in a sequential manner, with dosing of subjects in Cohort 2 (moderate hepatic impairment) and Cohort 3 (severe hepatic impairment) proceeding after review of safety and available preliminary PK data from hepatic impaired subjects in the previous cohorts. Based on the cumulative review of safety and PK data, sequential cohorts may or may not be initiated at the discretion of the investigator and Sponsor.

If necessary, replacement subjects may be enrolled if subjects do not complete all intensive PK procedures with Sponsor approval. Replacement subjects will not be enrolled for subjects who discontinue the study due to treatment-related AEs.

The study design is presented in Figure 1-1.

Figure 1-1. Cohorts 1, 2, and 3 Study Schema



Each of the three cohorts will consist of two groups:

- **Group 1** (test, N = 10): Subjects with mild/moderate/severe hepatic impairment
- **Group 2** (reference, N = 10): Subjects with normal hepatic function

Safety will be evaluated by assessment of physical examinations, vital signs, clinical laboratory tests and ECGs at various time points during the study, and by documentation of AEs.

PK Assessments

Plasma PK Collection

Intensive PK sampling will occur relative to dosing of GS-9674 at the following time points for each cohort:

- **Day 1**: -0.5, 0 (pre-dose, ≤ 5 minutes prior to dosing), 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, 24, 48, 72, and 96 hours post-dose

Plasma concentrations of GS-9674 (and its metabolites, as applicable) will be determined and PK evaluated. PK parameters will be estimated, as appropriate.

In addition, on Day 1 at the 3 and 5 hours post dose time-points, additional plasma samples will be collected for plasma protein binding evaluation. Alternatively, pre-dose samples may be utilized for plasma protein binding evaluation.

A blood sample for PK analysis will also be collected at the Early Termination (ET) visit (if applicable) and may be analyzed.

PD Assessments

Plasma and/or Serum PD Collection

Blood samples will be collected relative to dosing of GS-9674 or PTM to measure PD biomarkers including but not limited to FGF19 (fibroblast growth factor 19) and 7-alpha-hydroxy-4-cholesten-3-one (C4) for GS-9674 at the following time points for each cohort:

- **Day -1**: -0.5, 0 (predose, ≤ 5 minutes prior to dosing), 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, and 16 hours post-dose (relative to Day 1 dosing time)

- **Day 1**: -0.5, 0 (pre-dose, ≤ 5 minutes prior to dosing), 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, 24, 48, 72, and 96 hours post-dose

A single blood sample will be collected for analysis including but not limited to bile acids at the following time point:

- **Day 1**: -0.5 hours predose

A blood sample for PD analysis will also be collected at the ET visit (if applicable) and may be analyzed.

Safety Assessments

- Complete Physical exam: Screening and ET visit (if applicable)

- Symptom-directed physical exam: Days -2, 5, and FU visit

- Vital signs (blood pressure, pulse, respiration rate, and temperature): Screening, Days -2, 1 (predose and at approximately 3 hours postdose), 5, and FU visit or ET visit (if applicable)

- Height, Weight, and BMI: Screening

- Clinical Laboratory Tests (hematology, fasting chemistry, and urinalysis): Screening, Days -2 (two sets of safety labs will be collected upon clinic admission; one will be sent to the central lab and another will be sent to the sites' local lab to obtain results in time for enrollment on Day 1), 5, and FU visit or at ET visit (if applicable)

- Coagulation (PT, PTT, INR): Screening and FU Visit

- Urine drug/alcohol assessment: Screening, Day -2, and at the FU visit or at ET visit (if applicable).
- 12-lead ECG: Screening, Days -2, 5, and at the FU visit or ET visit (if applicable)
- Serum Pregnancy Test (female subjects of childbearing potential): Screening
- Urine Pregnancy Test (female subjects of childbearing potential): Days -2, 5, and at the FU visit or at ET visit (if applicable)
- FSH (female subjects ≤ 54 years old with amenorrhea > 12 months): Screening
- Serology (Hepatitis B surface antigen [HBVsAg], Hepatitis C antibody [HCV-Ab], Human immunodeficiency virus [HIV]-1/2): Screening
- Assessment of AEs and concomitant medications will continue throughout the study.

Additional details regarding study assessments can be found in Section 13.

1.4. Sample Size and Power

For each cohort, with 16 (8 per group) evaluable subjects, the estimated upper limit of one-sided 95% confidence intervals (CIs) of the geometric least squares mean (GLSM) ratio of (mild, moderate or severe) hepatic impaired group vs. control (normal hepatic function), with regards to AUC_{last}, AUC_{inf}, and C_{max}, would be less than 200% with ≥ 88% probability, if the estimated GLSM ratio were 1.0. This is assuming a standard deviation (SD) of no more than 0.463 on a natural logarithm scale, supported by previous Gilead study GS-US-402-1851. With 25% overage, a total sample size of 60 subjects (10 per group, 20 per cohort) will be required.

2. TYPE OF PLANNED ANALYSIS

2.1. Data Monitoring Committee Analyses

This study does not have a data monitoring committee (DMC). Therefore, no analyses will be conducted for the DMC.

2.2. Interim Analysis

No interim analysis is planned.

2.3. 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 final analysis of the data will be performed.

2.4. Changes from Protocol-Specified Analysis

No changes from protocol-specified analyses are planned.

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

By-subject listings will be presented for all subjects in the All Enrolled Analysis Set, and sorted by subject identification (ID) number in ascending order, visit date, and time (if applicable), unless otherwise specified. Data collected on log forms, such as AEs, will be presented in chronological order within subject. The treatment group to which subjects were initially assigned 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 will be provided in the disposition table as detailed in Section 4. A listing of reasons for exclusion from analysis sets will be provided by subject.

3.1.1. All Enrolled Analysis Set

The All Enrolled Analysis Set includes all subjects who received a study subject identification number in the study after screening.

This is the primary analysis set for safety listings.

3.1.2. Safety Analysis Set

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

3.1.3. Pharmacokinetic Analysis Sets

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

3.1.4. Pharmacodynamic Analysis Sets

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

3.2. Strata and Covariates

This study does not use a stratified randomization schedule in enrolling subjects. No covariates will be included in the analyses.

3.3. Examination of Subject Subsets

There are no prespecified subject subsets for analyses.

3.4. Multiple Comparisons

All endpoint tests will be done at the significance level of 0.05 with no multiplicity adjustments made for testing.

3.5. Missing Data and Outliers

3.5.1. Missing Data

In general, missing data will not be imputed unless methods for handling missing data are specified. Exceptions are presented in this document.

The handling of missing or incomplete dates for AE onset is described in Section 7.1.6.2.

3.5.2. Outliers

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

3.6. Data Handling Conventions and Transformations

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 enrollment date will be used instead of the first dosing date of study drug. 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 lower LOQ will be used to calculate descriptive statistics if the datum is reported in the form of "< x" (where x is considered the lower LOQ). For example, if the values are reported as < 50 and < 5.0, values of 49 and 4.9, respectively, will be used to calculate summary statistics. An exception to this rule is any value reported as < 1 or < 0.1, a value of 0.9 or 0.09, respectively, will be used to calculate summary statistics.

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

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

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 logarithmic transformation will be used for analyzing concentrations and PK parameters. Concentration values that are below the limit of quantitation (BLQ) will be presented as "BLQ" in the concentration data listing. Values that are BLQ will be treated as 0 at predose time points and one-half the value of the LOQ at postdose time points for summary purposes.

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

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

3.7. Visit Windows

3.7.1. Definition of Predose, Postdose and Study Day

Predose value is defined as the last available off-treatment value collected prior to the first dose of study drug.

Postdose value is defined as any value collected after the first dose of study drug and before the date of the last dose of study drug plus 30 days.

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.

3.7.2. Analysis Visit Windows

The nominal visit as recorded on the CRF will be used when data are summarized by visit. Any data relating to unscheduled visits will not be assigned to a particular visit or time point and in general will not be included in summaries. However, the following exceptions will be made:

- An unscheduled visit prior to the first dose of study drug may be included in the calculation of predose 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 discontinue from the study, early termination (ET) data will be summarized as a separate visit, labeled as "Early Termination."
- Data collected on a follow-up visit will be summarized as a separate visit, and labeled "Follow-up."
- Data obtained after the follow-up visit or last dose date plus 30 days (whichever is later) will be excluded from the summaries, but will be included in the listings.

3.7.3. Selection of Data in the Event of Multiple Records on the Same Day

Depending on the statistical analysis method, single values may be required for each day. For example, change from predose by visit usually requires a single value.

If multiple, valid, nonmissing numeric observations exist on a day, records will be chosen based on the following rules if a single value is needed:

- For predose, the last available record on or prior to the date and time 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, average (arithmetic or geometric mean, as appropriate) will be used for the predose value.

- For postdose visits:

  — 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 observations exist on a day, records will be chosen based on the following rules if a single value is needed:

- For predose, the last available record on or prior to the date and time 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 postdose values, follow the same rules described above for postbaseline numeric observations, except that if there are multiple records on the same day, the most conservative value 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 and disposition will be provided by hepatic function group and by hepatic function group within cohort. This summary will present the number of subjects enrolled, and the number and percentage of subjects in each of the categories listed below. For the Safety Analysis Set category, the denominator for the percentage calculation will be the total number of subjects enrolled for each column. For all other categories, the denominator for the percentage calculation will be the total number of subjects in the Safety Analysis Set for each column.

- Safety Analysis Set
- PK Analysis Set for each analyte
- PD Analysis Set for each biomarker
- Completed study drug
- Did not complete study drug with reason for premature discontinuation of study drug
- Completed the study
- Did not complete the study with reason for premature discontinuation of study

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

The following by-subject 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

A by-subject listing of subject disposition including cohort, hepatic function group, date of the last dose of study drug (study days), study drug completion status, reason for study drug discontinuation, study completion status, reason for study discontinuation, PK set status (indicating whether or not a subject is included in a PK analysis set), and PD set status will be provided by subject ID number in ascending order.

4.2. Extent of Exposure

A subject's extent of exposure to study drug data will be generated from the study drug administration page in the eCRF. Exposure data will be listed.

4.3. Protocol Deviations

A by-subject listing will be provided for those subjects who did not meet at least 1 eligibility (inclusion or exclusion) criterion. The listing will present the entry criterion (or criteria if more than 1 violation) that subjects did not meet and related comments, if collected.

Protocol deviations occurring after subjects entered the study are documented during routine monitoring. Any deviations identified will be evaluated to determine if it justifies excluding the subject from any analysis sets.

5. BASELINE CHARACTERISTICS

5.1. Demographics

Subject demographic variables (ie, age, sex, race, and ethnicity) will be summarized by hepatic function group and by hepatic function group within cohort using descriptive statistics for age, and using numbers and percentages of subjects for sex, race, and ethnicity. The summary of demographic data will be provided for the Safety Analysis Set.

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

5.2. Baseline Characteristics

Baseline characteristics include body weight (in kg), height (in cm), and body mass index (BMI; in kg/m2), calculated creatinine clearance (CLcr; in mL/min) by Cockcroft-Gault method {Cockcroft 1976}, and CPT score. These baseline characteristics will be summarized by hepatic function group and by hepatic function group within cohort using descriptive statistics for continuous variables and using number and percentage of subjects for categorical variables. For baseline body weight, height, and BMI, descriptive statistics will also be presented by sex in the same table. CPT score will be summarized for hepatic impaired subjects only by presenting the number and percentage of subjects in each score category. The summary of baseline characteristics will be provided for the Safety Analysis Set. No formal statistical testing is planned.

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

5.3. Medical History

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

A by-subject listing of general medical history will be provided by subject ID number in ascending order. The listing will include relevant medical condition or procedure reported term, onset date, ongoing status, and resolution date (if applicable).

6. EFFICACY ANALYSES

Efficacy will not be evaluated in the study.

7. SAFETY ANALYSES

7.1. Adverse Events and Deaths

7.1.1. Adverse Event Dictionary

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

7.1.2. Adverse Event Severity

Adverse events are graded by the investigator as Grade 1, 2, 3, or 4 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 presented last in the summary presentation.

7.1.3. Relationship of Adverse Events to Study Drug

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 from that captured on the CRF.

7.1.4. Relationship of Adverse Events to Study Procedure

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

7.1.5. Serious Adverse Events

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

7.1.6. Treatment-Emergent Adverse Events

7.1.6.1. Definition of Treatment Emergent

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.

7.1.6.2. 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 date of first dose 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 date of the first dose 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.

7.1.7. Summaries of Adverse Events and Deaths

Treatment-emergent AEs will be summarized based on the Safety Analysis Set.

The number and percentage of subjects who experienced at least 1 TEAE will be provided and summarized by SOC, PT, and hepatic function group as follows:

- All TEAEs
- TEAEs of Grade 3 or above
- TEAEs of Grade 2 or above
- All TEAEs by severity
- All TE treatment-related AEs

- All TE treatment-related AEs by severity
- All TEAEs related to study procedures
- 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

A brief, high-level summary of AEs described above will be provided by hepatic function 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 then by PT in descending order of total frequency within each SOC. For summaries by severity, the maximum severity will be used for those AEs that occurred more than once in an individual subject during the study.

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

- All AEs, indicating whether the event is treatment emergent
- SAEs
- Deaths
- AEs leading to premature discontinuation of study drug
- AEs leading to discontinuation of study

7.1.8. Additional Analysis of Adverse Events

No additional analysis of adverse events is planned.

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. The analysis will be based on values reported in conventional units. When values are BLQ, they will be listed as such, and the imputed value will be used for the purpose of calculating summary statistics. 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 on the Gilead Grading Scale for Severity of Adverse Events and Laboratory Abnormalities 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 hepatic function group for each laboratory test specified in the study protocol as follows:

- Predose values
- Values at each postdose visit
- Change from predose at each postdose visit

Predose and postdose values will be defined as described in Section 3.7.1. Change from predose to a postdose visit will be defined as the visit value minus the predose value. The mean, median, Q1, Q3, minimum, and maximum values will be displayed to the reported number of digits; SD values will be displayed to the reported number of digits plus 1.

In the case of multiple values in an analysis window, data will be selected for analysis as described in Section 3.7.3.

7.2.2. Graded Laboratory Values

The Gilead Grading Scale for Severity of Adverse Events and Laboratory Abnormalities 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 predose at any postdose visit, up to and including the date of last dose of study drug plus 30 days for subjects who permanently discontinued study drug. If the relevant predose laboratory value is missing, any abnormality of at least Grade 1 observed within the time frame specified above will be considered treatment emergent.

7.2.2.2. Summaries of Laboratory Abnormalities

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

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

- Graded laboratory abnormalities
- Grade 3 or 4 laboratory abnormalities

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

A by-subject listing of treatment-emergent 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 displayed.

7.3. Vital Signs

Descriptive statistics will be provided by hepatic function group for vital signs as follows:

- Predose value
- Values at each postdose visit
- Change from predose at each postdose visit

Predose and postdose values will be defined as described in Section 3.7.1. Change from predose to a postdose visit will be defined as the postdose value minus the predose value.

In the case of multiple values in an analysis window, data will be selected for analysis as described in Section 3.7.3. 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.

A summary of prior and concomitant medications will not be provided.

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. Investigator Electrocardiogram Assessment

A shift table of the investigators' assessment of ECG results at each visit compared with predose values will be presented by hepatic function 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 predose or postdose 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 by-subject listing of subject pregnancies during the study will be provided by subject ID number. No additional safety measures are specified in the protocol.

Although not necessarily related to safety, a by-subject listing of all comments received during the study on the comments form will be provided by subject ID number, and form for which the comment applies.

7.7. Changes From Protocol-Specified Safety Analyses

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

8. PHARMACOKINETIC EVALUATION/ANALYSIS

8.1. Estimation of Pharmacokinetic 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 zero.

For area under the curve (AUC), samples below the limit of quantitation (BLQ) of the bioanalytical assays occurring prior to the achievement of the first quantifiable concentration will be assigned a concentration value of zero 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_{inf}, 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. Pharmacokinetic Parameters

Pharmacokinetic parameters will be generated for all subjects for whom parameters can be derived. The analytes presented in Table 8-1 will be evaluated if data are available.

Table 8-1. Study Treatments and Associated Analytes

Cohort	Treatment	Analytes
1 and 2	A single oral dose of GS-9674 30 mg (3 × 10 mg tablet) administered on Day 1	GS-9674 and its metabolite GS-716070, GS-1056756 and GS-1056757, as applicable
3	A single oral dose of GS-9674 10 mg (1 × 10 mg tablet) administered on Day 1	GS-9674 and its metabolite GS-716070, GS-1056756 and GS-1056757, as applicable

The analytes and parameters presented in Table 8-2 will be used to evaluate the PK objectives of the study. The primary PK parameters are AUC_{last}, AUC_{inf}, and C_{max} of GS-9674. The PK parameters to be estimated in this study are listed and defined in the Pharmacokinetics Abbreviations section.

Table 8-2. Pharmacokinetic Parameters for Each Analyte

Analyte	Parameters
GS-9674, and its metabolite GS-716070, GS-1056756 and GS-1056757, as applicable	$\%AUC_{exp}$, AUC_{last}*†, AUC_{inf}*†, C_{max}*†, C_{last}, T_{max}, T_{last}, λ_z, CL/F†, V_z/F, and $t_{1/2}$, as appropriate

* Parameter used in sample size and power calculations.
† May be calculated as both total and unbound.

8.3. Statistical Analysis Methods

8.3.1. General Considerations

Individual subject concentration data and individual subject PK parameters (including percentage of protein binding) for GS-9674, GS-716070, GS-1056756 and GS-1056757 will be listed and summarized using descriptive statistics by hepatic function group within cohort. Summary statistics (numbers of subjects, mean, SD, coefficient of variation [%CV], median, minimum, maximum, Q1, and Q3) will be presented for both individual subject concentration data by time point and individual subject PK parameters by hepatic function group within cohort. 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.

The percentage unbound fraction (f_u) for each analyte (where applicable) will be estimated by averaging the percentage unbound in plasma from 3 hour postdose, 5 hour postdose, and spike-in samples. Individual subject unbound PK parameter estimates for AUC_{inf}, AUC_{last}, C_{max} may be calculated using PK parameter estimates multiplied by f_u. The unbound CL/F may also be calculated by using the estimated CL/F divided by f_u.

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 zero 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 parameters can be derived. The sample size for each PK parameter will be based on the number of subjects with nonmissing data for that PK parameter.

The following tables will be provided for each analyte by hepatic function group within each cohort:

- Individual subject concentration data and summary statistics
- Individual subject plasma PK parameters (total) and summary statistics

- Individual subject f_u and unbound PK parameters (as applicable) based on protein binding and summary statistics

- Percentage of unbound and bound GS-9674, GS-716070, and GS-1056756 at 3 hours postdose, 5 hours postdose, and spike-in samples

- Spearman's rank correlation coefficient between selected PK parameter estimates (AUC_{last}, AUC_{inf}, and C_{max}) and overall CPT Score, albumin, total bilirubin, prothrombin time, International Normalized Ratio, and serum creatinine

The following figures will be provided for each analyte by hepatic function group within each cohort:

- Individual subject concentration data versus time (on linear and semilogarithmic scales)

- Mean (± SD) concentration data versus time (on linear and semilogarithmic scales)

- Median (Q1, Q3) concentration data versus time (on linear and semilogarithmic scales)

- Scatter plots to show the relationship between dose-normalized PK parameter estimates (AUC_{inf}, AUC_{last}, and C_{max}) and overall CPT score, serum albumin, total bilirubin, prothrombin time, International Normalized Ratio, and serum creatinine. This set of plots may also be provided for overall enrolled subjects.

Individual, mean, and median postdose concentration values that are ≤ LLOQ will not be displayed in the figures and remaining points connected. Dose normalization is calculated by dividing the PK parameter value by the ratio of the test dose/reference dose. The reference dose is 30 mg.

The following listings will be provided:

- PK sampling details by subject, including procedures, differences in scheduled and actual draw times, and sample age

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

- Individual data on protein binding

8.3.2. Statistical Methodology

The statistical comparisons of the natural log-transformed PK parameters for each analyte and hepatic function group comparison of interest will be based on the PK analysis set for the analyte under evaluation. For each analyte, all subjects with available data for the PK parameter under evaluation will be included in the modeling.

Comparisons of interest are shown in Table 8-3.

Table 8-3. Statistical Comparisons for Pharmacokinetic Analyses of Normal and Impaired Hepatic Function

Analyte	Parameter	Comparison	
		Test	Reference
GS-9674, GS-716070, GS-1056756 and GS-1056757	AUC_{last}	Mild hepatic impairment	Matched normal hepatic function
	AUC_{inf}		
	C_{max}		
	AUC_{last}	Moderate hepatic impairment	Matched normal hepatic function
	AUC_{inf}		
	C_{max}		
	AUC_{last}	Severe hepatic impairment	Matched normal hepatic function
	AUC_{inf}		
	C_{max}		

For each analyte and each PK parameter within each cohort, a parametric (normal theory) ANOVA will be fitted to the natural log-transformed values of the single dose PK parameter under evaluation.

The statistical model will include hepatic function group as a fixed effect. The following SAS® PROC MIXED code will provide the comparison between the hepatic function groups and the 90% CI calculations for natural log-transformed PK parameters.

```
proc mixed;
  by cohort analyte paramcd;
  class hepaticgrp subjid;
  model lnest = hepaticgrp / ddfm=kr s;
  repeated / group=hepaticgrp;
  lsmeans hepaticgrp / e diff cl alpha = 0.1;
  estimate 'Mild impairment vs Normal' hepaticgrp 1  -1 / cl alpha = 0.1;
  (estimate 'Moderate impairment vs Normal' hepaticgrp 1 -1 / cl alpha = 0.1;)
  (estimate 'Severe impairment vs Normal' hepaticgrp -1 1 / cl alpha = 0.1;)
  ods output Estimates = LS_Diffs LSMeans = LS_Means CovParms = MSE;
run;
```

The ESTIMATE statement will be used to produce the point estimate and the corresponding 90% CI of the difference in PK parameters of interest on a logarithmic scale. The test-to-reference ratio and associated 90% CI will be calculated by exponentiation of the point estimate and the corresponding lower and upper limits, which is consistent with the two 1-sided tests approach {U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) 2003}, {U.S. Department of Health and

Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) 2001}.

If the upper bound of the 2-sided 90% CI of the GLSM ratio for AUC_{last}, AUC_{inf}, and C_{max} is smaller than 2.0, we will reject the hypothesis that subjects with hepatic impairment exhibit average PK parameter (ie, AUC_{last}, AUC_{inf}, and C_{max}) increases of at least 100% for GS-9674 compared to subjects with normal hepatic function.

Nonparametric Analysis

Nonparametric analyses for the PK parameters (if calculated) CL/F, V_Z/F, and $t_{1/2}$, may be performed using the Wilcoxon rank sum test for parallel design between the test and reference groups for GS-9674, GS-716070, GS-1056756 and GS-1056757.

```
data param;
  set adam.param;
  where cohort=1 and analyte='GS-9674' and param='CL/F';
run;

proc npar1way data=param wilcoxon;
  class hepaticgrp;
  var result;
run;
```

8.4. Sensitivity Analysis

Sensitivity analysis may be conducted for the key PK analyses if the PK scientist identifies PK data as questionable. The sensitivity analysis will exclude specific data from analyses, if appropriate. If a sensitivity analysis is deemed necessary, a listing of the PK parameter(s) data being excluded, with associated reason(s) provided by the PK scientist, will be generated.

9. PHARMACODYNAMIC EVALUATION/ANALYSIS

9.1. Estimation of Pharmacodynamic Parameters

PD parameters will be calculated for FGF19 and C4 on Days -1, and 1. In particular AUC calculations will be based on the linear trapezoidal rule, summing trapezoids over the particular time period (0 – 24 hours or x – y hours) on a particular day. C_{max}, C_{min}, T_{max}, and T_{min} will be determined empirically for the data.

9.2. Pharmacodynamic Parameters

PD parameters in

Table 9-1 will be generated for all subjects for whom parameters can be derived for biomarkers, FGF19 and C4, if data are available.

Table 9-1. Pharmacodynamic Parameters for FGF19 and C4

Day	Parameter
-1	AUC_{0-24}
1	AUC_{0-24}
1	AUC_{0-24} ratio: $AUC_{0-24, (Day\ 1)}$ / $AUC_{0-24,(Day-1)}$
-1	$AUC_{Partial}$
1	$AUC_{Partial}$
1	$AUC_{Partial}$ ratio: $AUC_{Partial, (Day\ 1)}$ / $AUC_{Partial,(Day-1)}$
-1	C_{min}
1	C_{min}
1	$C_{min,}$ ratio: $C_{min, (Day\ 1)}$ / $C_{min, (Day\ -1)}$
-1	C_{max}
1	C_{max}
1	C_{max} ratio: $C_{max, (Day\ 1)}$ / $C_{max, (Day\ -1)}$
-1	T_{min}
1	T_{min}
1	T_{min} ratio: $T_{min, (Day\ 1)}$ / $T_{min, (Day\ -1)}$
-1	T_{max}
1	T_{max}
1	T_{max} ratio: $T_{max, (Day\ 1)}$ / $T_{max, (Day\ -1)}$

1 AUC_{0-24} Area under the curve calculated by the trapezoidal rule for the time from 0 to 24 hours for the day given in the first column. For Day -1, take -0.5 and 0 hours of Day 1 as 23.5 and 24 hours of Day -1.
2 $AUC_{partial}$ (AUC_{2-8} and AUC_{2-12}) Area under the curve calculated by the trapezoidal rule for the time from 2 to 8 and 2 to 12 hours for the day given in the first column.
3 C_{max}, C_{min} Concentration of FGF19 at the maximum or C4 at the minimum respectively for each subject from 0 to 24 hours for the day given in the first column. For Day -1, take -0.5 and 0 hours of Day 1 as 23.5 and 24 hours of Day -1.
4 T_{max}, T_{min} Time of maximum or minimum concentration of FGF19 or C4 respectively for each subject from 0 to 24 hours for the day given in the first column. For Day -1, take -0.5 and 0 hours of Day 1 as 23.5 and 24 hours of Day -1.

9.3. Statistical Analysis Methods

9.3.1. General Considerations

Individual subject concentration data and individual subject PD parameters shown in Table 9-1 will be listed and summarized using descriptive statistics by hepatic function group within each cohort. Summary statistics (numbers of subjects, geometric mean, 95% CI, %CV, median, minimum, maximum, Q1, and Q3) will be presented at specific time points as shown in Table 9-1.

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.

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

The following tables will be provided for each biomarker by hepatic function group within each cohort:

- PD concentrations and summary statistics
- PD parameters and summary statistics

The following figures will be provided for each biomarker by hepatic function group within each cohort:

- Mean (± SD) concentration data versus time on a linear (and semilogarithmic) scale for days -1 and 1.
- Boxplots of AUCs and AUC ratios as indicated in Table 9-1 on a linear (and logarithmic) scale, categorized by days -1 and 1, and by hepatic function group.
- Boxplots of C_{max} and C_{max} ratios as indicated in Table 9-1 on a linear (and logarithmic) scale, categorized by days -1 and 1, and by hepatic function group.
- Boxplots of C_{min} and C_{min} ratios as indicated in Table 9-1 on a linear (and logarithmic) scale, categorized by days -1 and 1, and by hepatic function group.

The following listings will be provided:

- PD sampling details by subject, including procedures, differences in scheduled and actual draw times, and sample age.

9.3.2. Statistical Methodology

The statistical comparisons of the natural log-transformed PD parameters for each biomarker and treatment comparison of interest will be performed. The statistical modeling will be based on the PD analysis set for the biomarker under evaluation. For each biomarker, all subjects with available data for the PD parameter under evaluation will be included in the modeling.

Treatment comparisons of interest are shown in Table 9-2.

Table 9-2. Statistical Comparisons for Pharmacodynamic Analyses

Treatment	Biomarker	Parameter	Comparison	
			Test	Reference
GS-9674	FGF19	Day 1 / Day -1: $AUC_{2\text{-}8}$, $AUC_{2\text{-}12}$, C_{max}	Mild Impairment	Matched normal hepatic function
	C4	Day 1 / Day -1: $AUC_{2\text{-}8}$, $AUC_{2\text{-}12}$, C_{min}		
	FGF19	Day 1 / Day -1: $AUC_{2\text{-}8}$, $AUC_{2\text{-}12}$, C_{max}	Moderate Impairment	Matched normal hepatic function
	C4	Day 1 / Day -1: $AUC_{2\text{-}8}$, $AUC_{2\text{-}12}$, C_{min}		
	FGF19	Day 1 / Day -1: $AUC_{2\text{-}8}$, $AUC_{2\text{-}12}$, C_{max}	Severe Impairment	Matched normal hepatic function
	C4	Day 1 / Day -1: $AUC_{2\text{-}8}$, $AUC_{2\text{-}12}$, C_{min}		

For each biomarker, each cohort and each PD parameter, a parametric (normal theory) mixed-effects ANOVA model will be fitted to the natural log-transformed values of the single and multiple dose PD parameter under evaluation using SAS® PROC MIXED.

The statistical model will include hepatic function group as a fixed effect. The following SAS PROC MIXED code will provide the hepatic function group comparison analysis and the 90% CI calculations for natural log-transformed PD parameters.

```
proc mixed;
  where biomarker ={‘C4} and param={‘Cmax};
  class hepaticgrp subjid;
  model lnest = hepaticgrp / ddfm=kr;
  repeated / group=hepaticgrp;
  lsmeans hepaticgrp / e diff cl alpha = 0.1;
  estimate ‘Mildly Impaired vs Normal’ hepaticgrp 1 -1 / cl alpha = 0.1;
  (estimate ‘Moderately Impaired vs Normal’ hepaticgrp 1 -1 / cl alpha = 0.1;)
  (estimate ‘Severely Impaired vs Normal’ hepaticgrp -1 1 / cl alpha = 0.1;)
  ods output Estimates = LS_Diffs LSMeans = LS_Means CovParms = MSE;
run;
```

The ESTIMATE statement will be used to produce the point estimate and the corresponding 90% CI of the difference in PD parameters of interest on a logarithmic scale. The test-to-reference ratio and associated 90% CI will be calculated by taking the exponential of the point estimate and the corresponding lower and upper limits, which is consistent with the two 1-sided tests approach {U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) 2003}, {U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) 2001}.

10. REFERENCES

Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16:31-41.

U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER). Guidance for Industry. Statistical Approaches to Establishing Bioequivalence. January, 2001.

U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER). Guidance for Industry. Bioavailability and Bioequivalence Studies for Orally Administered Drug Products - General Considerations (Revision 1). March, 2003.

11. SOFTWARE

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

Phoenix WinNonlin® 7.0. Pharsight Corporation, Princeton, NJ, USA.

nQuery Advisor(R) Version 6.0 or newer, Statistical Solutions, Cork, Ireland.

12. SAP REVISION

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

13. APPENDIX 1 SCHEDULE OF ASSESSMENTS

Study Procedure	Screen[a]	Day -2	Day -1	Day 1	Day 4	Day 5[b]	Day 10-14 FU Period	ET[d]
Written Informed Consent	X							
Medical History	X							
Complete Physical Exam	X							X
Symptom-directed Physical Examination[e]		X				X	X	
Height	X							
Weight	X							
BMI	X							
Vital Signs[f]	X	X		X		X	X	X
HIV-1, HBV, and HCV Testing[h]	X							
Hematology[g, h]	X	X				X	X	X
Serum Chemistry[h]	X	X				X	X	X
Coagulation	X						X	
α-fetoprotein	X							
Urinalysis	X	X				X	X	X
Serum Pregnancy Test[i]	X							
Urine Pregnancy Test[i]		X				X	X	X
FSH[j]	X							
Urine and Alcohol Drug Screen[h]	X	X					X	X
12-Lead ECG	X	X				X	X	X

Study Procedure	Screen[a]	Day -2	Day -1	Day 1	Day 4	Day 5[b]	Day 10-14 FU Period	ET[d]
Enrollment			X					
Placebo Administration			X					
GS-9674 Administration				X				
PK Assessments [k]				X				X
PD Assessments [l]			X	X				X
Genetic Sample [m]				X				
Review Study Restrictions	X	X				X	X	X
Clinic Confinement		X----------					----------X	
Review AEs & Concomitant Medications[n]	X	X----------					----------X	X	X

a Prospective subjects should be screened no more than 28 days prior to administration of the first dose of study drugs.

b Subjects will be discharged from the clinic on Day 5 following all morning assessments.

c Subjects will be required to return for a Follow-up visit 10-14 days after study drug dosing.

d Assessments will be performed within 72 hours of early termination from the study.

e Symptom-driven PEs will be performed on Day 1 (predose), 4, and at the Follow-up Visit

f Vital signs include blood pressure, pulse rate, respiration rate, and body temperature. To be performed on Day -2, 1 (predose and at approximately 3 hours postdose), 5, and at the Follow-up Visit.

g Hematology: CBC with differentials

h Fasting serum chemistry: alkaline phosphatase, AST, ALT, total bilirubin, direct and indirect bilirubin, GGT, total protein, albumin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorus, magnesium, potassium, sodium, uric acid, total cholesterol, HDL, LDL, triglycerides, and amylase (reflex lipase testing is performed in subjects with total amylase > 1.5 × ULN).

i Female subjects of child-bearing potential.

j Female subjects ≤ 54 years old with amenorrhea > 12 months as outlined in Protocol Appendix 3

k Intensive PK sampling will occur relative to the dosing at the following timepoints:

Day 1: -0.5, 0 (pre-dose, ≤ 5 minutes prior to dosing), 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, 24, 48, 72, and 96 hours post-dose

In addition, on Day 1 at the 3 and 5 hours post dose timepoints, an additional plasma sample will be collected for plasma protein binding evaluation

l Blood samples will be collected relative to dosing of GS-9674 to measure PD biomarkers for FGF19 and C4 at the following timepoints for each cohort:

Day -1: -0.5, 0 (pre-dose, ≤ 5 minutes prior to dosing), 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, and 16 (relative to Day 1 dosing time assignment)
Day 1: -0.5, 0 (pre-dose, ≤ 5 minutes prior to dosing), 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, 24, 48, 72, and 96 hours post-dose

A single blood sample will be collected on Day 1, -0.5 hours predose for the determination including but not limited to individual bile acids.

m For subjects who provide consent, an additional blood sample will be obtained. This sample should be collected on Day 1, but may be collected at any time during the study or at a separate post-study visit, if necessary.

n From the time of obtaining informed consent through the first administration of study drug, record all SAEs, as well as any non-serious adverse events related to protocol-mandated procedures on the AE eCRF

All other untoward medical occurrences observed during the screening period, including exacerbation or changes in medical history are to be captured on the medical history CRF. See Protocol Section 7 Adverse Events and Toxicity Management for additional details.

GS-US-402-3885 SAP

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Clinical Pharmacology eSigned	23-Apr-2019 15:40:02
PPD	Clinical Research eSigned	23-Apr-2019 16:00:01
PPD	Biostatistics eSigned	24-Apr-2019 18:04:59