



STATISTICAL ANALYSIS PLAN

Study Title: A Phase 1 Open-Label, Parallel-Group, Single-Dose Study to Evaluate the Pharmacokinetics of GS-0976 or Fenofibrate in Subjects with Normal and Impaired Hepatic Function

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CONFIDENTIAL AND PROPRIETARY INFORMATION

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LIST OF ABBREVIATIONS

%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
CFR	Code of Federal Regulations
CI	confidence interval
CLcr	creatinine clearance
CPT	Child-Pugh-Turcotte classification system
CRF	case report form
CSR	clinical study report
CV	coefficient of variation
DMC	data monitoring committee
ECG	electrocardiogram
eCRF	electronic case report form
ET	early termination
FSH	Follicle-stimulating hormone
FU	follow-up
Gilead	Gilead Sciences
GLSM	geometric least-squares mean
Hb	hemoglobin
HBVsAg	hepatitis B surface antigen
HCV-Ab	hepatitis C antibody
HIV	human immunodeficiency virus
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
INR	international normalized ratio
LLOQ	lower limit of quantitation
LT	lower-level term
LOQ	limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
PK	pharmacokinetics
PT	preferred term or prothrombin time
PTT	partial thromboplastin time

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
TBD	to be determined
TE	treatment emergent
TEAE	treatment-emergent adverse events
TFLs	tables, figures, and listings
TOST	two one-sided tests
TQT	thorough QT
ULN	upper limit of normal
WHO	World Health Organization

PHARMACOKINETIC 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}
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} /λ _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
C _{max}	maximum observed plasma/serum concentration of drug
F	estimated oral bioavailability of the drug (%), calculated as 100(AUC _{oral} × Dose _{iv})/(AUC _{iv} × Dose _{oral})
f _u	unbound fraction
t _{1/2}	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 _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-426-3988. This SAP is based on the study protocol amendment 2 dated 18 December 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 objectives of this study are as follows:

- To evaluate the single-dose pharmacokinetics (PK) of GS-0976 in subjects with normal hepatic function, and mild, moderate, or severe hepatic impairment
- To evaluate the single-dose PK of fenofibrate in subjects with normal hepatic function and mild hepatic impairment

The secondary objectives of this study are as follows:

- To evaluate the safety and tolerability of GS-0976 single dose administration in subjects with normal hepatic function, and mild, moderate, or severe hepatic impairment
- To evaluate the safety and tolerability of single dose fenofibrate administration in subjects with normal hepatic function and mild hepatic impairment

1.2. Study Endpoints

The primary endpoints are the PK parameters AUC_{last} , AUC_{inf} , and C_{max} of GS-0976 or fenofibric acid (and their metabolites, as applicable). Additional PK parameters calculated include: % AUC_{exp} , T_{max} , C_{last} , T_{last} , λ_z , CL/F , V_z/F , and $t_{1/2}$ as appropriate.

Secondary endpoints include the incidences of adverse events (AEs) and laboratory abnormalities.

1.3. Study Design

This is a Phase 1, open-label, single-dose, parallel-group, multi-center, PK study of GS-0976 or fenofibrate in subjects with impaired hepatic function and matched normal hepatic function (control) groups.

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

- 1) Cohort 1 and 4: mild hepatic impairment (CPT Class A; score of 5-6) and matching controls
- 2) Cohort 2: moderate hepatic impairment (CPT Class B; score of 7-9) and matching controls
- 3) Cohort 3: severe hepatic impairment (CPT Class C; score of 10-15) and matching controls

The control group will consist of matched healthy subjects with normal hepatic function. A subject with normal hepatic function may serve as a matched control in Cohorts 1 and 2 but may only serve as a matched control to one hepatic impaired subject within a cohort.

Up to 80 (20 per cohort, 10 per group) male and non-pregnant/non-lactating female subjects aged 18-70 years inclusive with impaired and normal hepatic function will be enrolled to ensure completion of 64 (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 ($\pm 15\%$; $18 \leq \text{BMI} \leq 36 \text{ kg/m}^2$) with a subject in the respective hepatic impairment group. Subjects with hepatic impairment must have the respective CPT classification at Screening, have a diagnosis of chronic (> 6 months) and stable hepatic impairment with no clinically significant changes within 3 months (or 90 days) prior to study drug administration (Day 1).

Following completion of Screening and Day 2 admission assessments, eligible subjects will be enrolled in one of four cohorts and will be administered the following study treatment on Day 1:

- Cohorts 1 and 2: A single oral dose of 20 mg GS-0976 (2×10 mg capsules)
- Cohort 3: A single oral dose of 5 mg GS-0976 (1×5 mg tablet)
- Cohort 4: A single oral dose of 48 mg fenofibrate (1×48 mg tablet)

Subjects will be confined to the study center beginning Day 2 until the completion of assessments on Day 5. Subjects will return for a follow-up (FU) visit on Day 13 (± 2 days).

In general, dosing in subjects with normal hepatic function will begin after a matched subject with hepatic impairment has completed all Day 1 PK assessments (eg, 96 hours postdose).

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

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

The study designs are presented in [Figure 1](#) and [Figure 2](#).

Figure 1. High-Level Study Schema

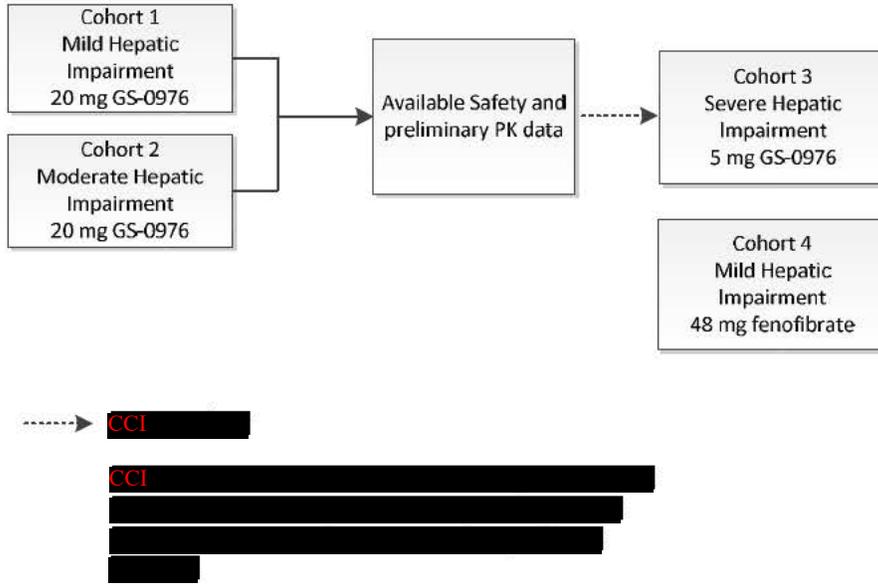
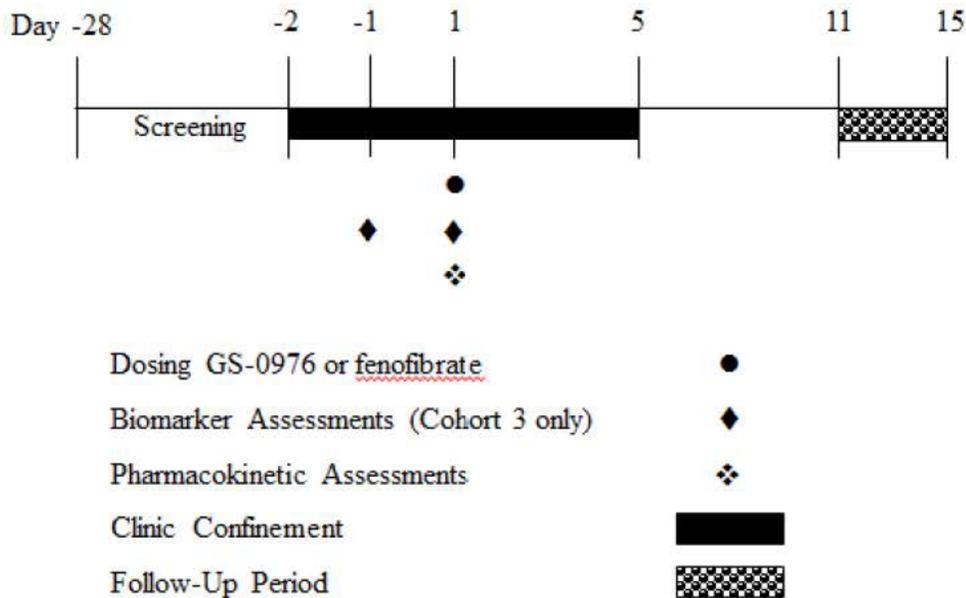


Figure 2. Cohort Study Schema



Each of the four cohorts will consist of two groups:

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

Safety will be evaluated by physical examinations, vital signs, clinical laboratory tests and electrocardiograms (ECGs) at various timepoints during the study, and by documentation of AEs.

PK Assessments

Plasma PK Collection

Intensive PK sampling will occur relative to dosing of GS-0976 or fenofibrate on Day 1 at the following time points for each cohort:

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

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

Plasma concentrations of GS-0976 or fenofibric acid (and their metabolites, as applicable) will be determined and PK evaluated. PK parameters will be estimated, as appropriate.

Protein Binding Samples

Plasma protein binding sampling will occur relative to dosing of GS-0976 or fenofibrate on Day 1 at the following time points for each cohort:

- Day 1: 1 and 3 hours post-dose

Plasma protein binding of GS-0976 or fenofibric acid (and their metabolites, as applicable) will be determined and summarized descriptively.

Exploratory Biomarker Assessments: CCI [REDACTED]

CCI [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

CCI

Safety Assessments

- Complete physical exam: Screening and at the early termination (ET) visit (if applicable).
- Symptom-driven physical exam: Day 2, Day 1 (prior to biomarker sample collection), Day 1 (predose and approximately 4 hours postdose), Day 5, and at the FU visit.
- Vital signs (blood pressure, heart rate, respiration rate, and body temperature): Screening, Day 2, Day 1 (prior to biomarker sample collection), Day 1 (predose and approximately 4 hours postdose), Day 5, and at the FU visit or ET visit (if applicable).
- Height, Weight, and BMI: Screening
- Clinical laboratory tests (hematology, chemistry, and urinalysis): Screening, Day 2, Day 1, Day 5, and at the FU visit or ET visit (if applicable).

Note: On Day 2 (clinic admission), two sets of safety labs will be collected. 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.

- Coagulation tests (prothrombin time [PT], partial thromboplastin time [PTT], international normalized ratio [INR]): Screening and at the FU visit or ET visit (if applicable).
- α -fetoprotein: Screening
- Urine drug and alcohol assessments: Screening, Day 2, and at the FU visit or ET visit (if applicable).
- 12-lead ECG: Screening, Day 2, Day 1 (predose and approximately 4 hours postdose), Day 5, and at the FU visit or ET visit (if applicable).
- Serum pregnancy test (female subjects of childbearing potential only): Screening and Day 2, Day 5, and at the FU visit or ET visit (if applicable).
- FSH (female subjects \leq 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 [Appendix 1](#).

1.4. Sample Size and Power

For Cohorts 1 to 3, with 16 (8 per group) evaluable subjects per cohort, the estimated upper limit of one-sided 95% CI 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_{inf} and C_{max} , would be less than 200% with $\geq 72\%$ and $\geq 57\%$ probability, respectively, if the estimated GLSM ratio were 1.0. This is assuming a standard deviation (SD) of no more than 0.588 for AUC_{inf} and 0.722 for C_{max} on a natural logarithmic scale, as supported by results from previous Study 0976-101. With 25% overage, a total sample size of 60 subjects (10 per group, 20 per cohort) will be required.

For Cohort 4, with 16 (8 per group) evaluable subjects, the estimated 2-sided 90% CI of the GLSM ratio of mild hepatic impaired group vs control (normal hepatic function), with regards to AUC_{last} , AUC_{inf} , and C_{max} would be within [0.5, 2.0] with $\geq 90\%$ probability, if the estimated GLSM ratio were 1.0. This is assuming a SD of no more than 0.387 on a natural logarithmic scale, as supported by information from the US Food and Drug Administration (FDA) {U. S. Food and Drug Administration 2004}. With 25% overage, a total sample size of 20 subjects (10 per group) 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 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.

3.2. 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

No multiplicity adjustments will be 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, etc. For values reported as < 1 or < 0.1, a value of 0.9 or 0.09, respectively, will be used to calculate summary statistics.
- A value that is 1 unit above the upper LOQ will be used to calculate descriptive statistics if the datum is reported in the form of “> x” (where x is considered the upper LOQ). Values with decimal points will follow the same logic as the bullet point above.
- The 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 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.”

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

3.7. Visit Windows

3.7.1. Definition of Predose, Postdose, Study Day

Predose value is defined as the last available off-treatment value collected on or prior to the date and time of 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 Visit”
- Data collected on a follow-up visit will be summarized as a separate visit, and labeled “Follow-up Visit.”
- Data obtained after the follow-up visit or last dose date plus 30 days (whichever is later) will be excluded from the summaries, but will be included in the listings.

The predose and postdose visits for laboratory tests are summarized in .

Table 3-1. Predose and Postdose Visits for Laboratory Tests

Cohort	Visit Label	Study Day
All	Predose	<= dose time on Study Day 1
	Day 5	5
	Follow-up	Follow-up

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 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 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 treatment, cohort, and hepatic function group. 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
- Completed 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 discontinuation

A by-subject listing of subject disposition including cohort, hepatic function group, date of the last dose of study drug(s) (study days), study completion status, reason for study discontinuation, and PK set status (indicating whether or not a subject is included in a PK analysis set) 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 eligibility 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 treatment, cohort, and hepatic function group using descriptive statistics for age, and using number and percentage of subjects for sex, race, and ethnicity. The summary of demographic data will be provided for the Safety Analysis Set.

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 (in kg), height (in cm), body mass index (BMI; in kg/m^2), creatinine clearance (CL_{cr} ; in mL/min) using the Cockcroft-Gault method {Cockcroft 1976}, and CPT score. These baseline characteristics will be summarized by treatment, cohort, and hepatic function group 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 the AEs met the definition of SAEs that was 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 (TE)

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. If the AE onset date is the same as the date of study drug start date then the AE onset time must be on or after the study drug start time. If the AE onset time is missing when the start dates are the same, the AE will be considered treatment emergent.
- 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, treatment, and hepatic function group as follows:

- All TEAEs
- TEAEs of Grade 3 or higher (by maximum severity)
- TEAEs of Grade 2 or higher

- 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

A brief, high-level summary of AEs described above will be provided by treatment and 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 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 treatment and 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, treatment, 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 treatment and hepatic function group for vital signs (systolic blood pressure, diastolic blood pressure, pulse, respiration rate, and temperature) 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. 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 concomitant medications will not be provided.

All 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 treatment and 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 deviations from the protocol-specified safety analyses.

8. PHARMACOKINETIC EVALUATION/ANALYSIS

8.1. Estimation of Pharmacokinetic Parameters

Pharmacokinetic (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 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 the 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 20 mg GS-0976 (2 × 10 mg capsules) administered on Day 1	GS-0976 and its metabolite GS-834773, as applicable
3	A single oral dose of 5 mg GS-0976 (1 × 5 mg tablet) administered on Day 1	GS-0976 and its metabolite GS-834773, as applicable
4	A single oral dose of 48 mg fenofibrate (1 × 48 mg tablet) administered on Day 1	fenofibric acid and its metabolite, 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-0976 or fenofibric acid (and their metabolites, as applicable). The PK parameters to be estimated in this study are listed and defined in the Pharmacokinetic Abbreviations section.

Table 8-2. Pharmacokinetic Parameters for Each Analyte

Analyte	Parameters
GS 0976 and fenofibric acid (and their metabolites, as applicable)	%AUC _{exp} , AUC _{last} ^b , AUC _{inf} ^{ab} , C _{max} ^{ab} , C _{last} , T _{max} , T _{last} , λ _z , CL/F ^b , V _z /F ^b , t _{1/2} , and metabolite to parent ratio (corrected for molecular weight) of AUC _{last} , AUC _{inf} , and C _{max} , as appropriate

a Parameter used in sample size and power calculations.

b 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-0976 and fenofibric acid (and their metabolites, as applicable) 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 will be estimated either by averaging the available 1 hour postdose and the 3 hour postdose percentage unbound in plasma or from spiked sample, where applicable. Individual subject unbound PK parameter estimates for AUC_{inf}, AUC_{last}, and C_{max} may be calculated using PK parameter estimates multiplied by f_u . The unbound CL/F may also be calculated by dividing the estimated CL/F by f_u . Unbound V_z/F may be calculated similarly.

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

- Individual percentage of unbound and bound GS-0976 and its metabolite GS-834773 with summary statistics for each timepoints (1 and 3 hour and spike) and the individual average bound and unbound percentage with summary statistics
- Spearman's rank correlation coefficient between selected PK parameter estimates (AUC_{last} , AUC_{inf} , and C_{max}) and overall CPT Score, albumin, total bilirubin, direct bilirubin, indirect bilirubin, prothrombin time, and INR

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 (\pm 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, direct bilirubin, indirect bilirubin, PT, and INR. This set of plots may also be provided for overall enrolled subjects.

Individual, mean, and median postdose concentration values that are \leq LLOQ will not be displayed in the figures, and the remaining points will be connected. Dose normalization is calculated by dividing the PK parameter value by the ratio of the test dose/reference dose. The reference dose is 20 mg for GS-0976. Dose normalization will not be performed for fenofibric acid.

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-0976 and its metabolite GS-834773	AUC _{last}	Mildly Impaired	Matched Normal
	AUC _{inf}		
	C _{max}		
	AUC _{last}	Moderately Impaired	Matched Normal
	AUC _{inf}		
	C _{max}		
	AUC _{last}	Severely Impaired	Matched Normal
	AUC _{inf}		
	C _{max}		
fenofibric acid and metabolites, as applicable	AUC _{last}	Mildly Impaired	Matched Normal
	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;
  repeated / group hepaticgrp;
  lsmeans hepaticgrp / e diff cl alpha 0.1;
  estimate 'Impaired vs Normal' hepaticgrp 1 -1 / cl alpha 0.1;
  * Adjust contrast accordingly based on the alphabetical order of the hepatic function groups
  being compared;
  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 ratios for AUC_{last} , AUC_{inf} , and C_{max} is less than 200%, 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 the study drug received compared with 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 each analyte.

```
data param;  
  set adam.param;  
  where cohort 1 and analyte 'GS-0976' and param 'CL/F';  
run;
```

```
proc npar1way data param wilcoxon;  
  class hepaticgrp;  
  var est;  
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. REFERENCES

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

U. S. Food and Drug Administration. Center for Drug Evaluation and Research. Tricor (Fenofibrate) Tablets. Application Number: 21-656. Clinical Pharmacology and Biopharmaceutics Review(s). Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2004/021656s000_TricorT OC.cfm. 05 November, 2004.

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.

10. SOFTWARE

SAS[®] Software Version 9.4. 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.

11. SAP REVISION

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

12. APPENDIX 1 SCHEDULE OF ASSESSMENTS

Appendix 1. Schedule of Assessments

Study Procedure	Screen ^a	Day -2	Day -1	Day 1	Days 2-4	Day 5 ^b	Day 13 (± 2 days) ^c	ET ^d
Written Informed Consent	X							
Medical History	X							
Complete Physical Exam	X							X
Symptom-Driven Physical Examination ^e		X	X ^q	X ^f		X	X	
Height, Weight, BMI	X							
Vital Signs ^g	X	X	X ^q	X ^f		X	X	X
HIV-1, HBV, and HCV Testing	X							
Hematology ^h	X	X ^k		X		X	X	X
Chemistry ^h	X	X ^k		X		X	X	X
Coagulation ^h	X						X	X
α-fetoprotein	X							
Urinalysis	X	X ^k		X		X	X	X
Serum Pregnancy Test ⁱ	X	X ^k				X	X	X
FSH ^j	X							
Urine Drug and Alcohol Screen	X	X ^k					X	X
12-Lead ECG	X	X		X ^f		X	X	X
Enrollment			X ^l	X				
Study Drug Administration				X				
PK Assessments ^m				X				X
Biomarker Assessments ^p			X	X				

Study Procedure	Screen ^a	Day -2	Day -1	Day 1	Days 2-4	Day 5 ^b	Day 13 (± 2 days) ^c	ET ^d
CCI								
Review Study Restrictions	X	X				X	X	X
Clinic Confinement				X				
Review AEs & Concomitant Medications ^o					X			

- a Prospective subjects should be screened no more than 28 days prior to administration of the first dose of study drug.
- b Subjects will be discharged from the clinic on Day 5, following all morning assessments.
- c Subjects will return for a follow up visit on Day 13 (± 2 days).
- d Assessments will be performed within 72 hours of early termination from the study.
- e Symptom driven PEs will be performed during confinement as needed, based on reported signs and symptoms.
- f Predose and approximately 4 hours postdose
- g Vital signs include blood pressure, heart rate, respiration rate, and body temperature.
- h Hematology, Chemistry, Coagulation: See Protocol Section 6.10.5.1 for specifics.
- i Female subjects of child bearing potential only.
- j Female subjects ≤ 54 years old with amenorrhea > 12 months as outlined in Protocol Appendix 2
- k 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.
- l Subjects of Cohort 3 will be enrolled on Day 1.
- m Intensive PK sampling will occur relative to dosing of GS 0976 or fenofibrate on Day 1 at the following time points for each cohort:
Day 1: 0 (pre dose, ≤ 5 minutes prior to dosing), 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 16, 24, 48, 72, and 96 hours post dose
 A blood sample for PK analysis will be collected at the Early Termination (ET) visit (if applicable) and may be analyzed.
 Plasma protein sampling will occur relative to dosing of GS 0976 or fenofibrate on Day 1 at the following time points for each cohort:
Day 1: 1 and 3 hours post dose
- n [REDACTED]
- o From the time of obtaining informed consent through the first administration of study drug, record all SAEs, as well as any nonserious AEs related to protocol mandated procedures on the AE CRF/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/eCRF. See Protocol Section 7, Adverse Events and Toxicity Management for additional details.
- p Biomarker sampling will be collected relative to the planned or actual dosing time of GS 0976 at the following time points for Cohort 3 only:
Day 1: 0, 1, 2, 3, 4, 6, 8, 12, and 16 hours postdose (relative to planned Day 1 dosing time)
Day 1: 0 (*pre dose, ≤ 5 minutes prior to dosing), 1, 2, 3, 4, 6, 8, 12, 16, and 24 hours postdose
 * Pre dose sample on Day 1 will also serve as 24 hour postdose sample on Day 1.
- q Prior to biomarker sample collection (Cohort 3 only)

GS-US-426-3988-SAP

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd- <small>MMM</small> - <small>yyyy</small> hh:mm:ss)
PPD	Clinical Pharmacology eSigned	11-Sep-2019 15:50:46
PPD	Clinical Research eSigned	11-Sep-2019 16:33:18
PPD	Biostatistics eSigned	12-Sep-2019 00:37:36