STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety, Tolerability, and Efficacy of GS-0976 in Subjects with Nonalcoholic Steatohepatitis
Name of Test Drug:	GS-0976
Study Number:	GS-US-426-3989
Protocol Version (Date):	Amendment 1.1: 19 December 2016
Analysis Type:	Final Analysis
Analysis Plan Version:	Version 1.0
Analysis Plan Date:	21 July, 2017
Analysis Plan Author(s):	PPD

CONFIDENTIAL AND PROPRIETARY INFORMATION

TABLE OF CONTENTS

LIST OF TABLES

LIST OF ABBREVIATIONS

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate transaminase
ATC	anatomical therapeutic chemical
AUC	area under the concentration
BLQ	below the limit of quantitation
BMI	body mass index
CI	confidence interval
CK18	cytokeratin (C18)
CLDQ	chronic liver disease questionnaire
CRF	case report form
CRP	C reactive protein
CSR	clinical study report
CTCAE	common terminology criteria for adverse events
DBP	diastolic blood pressure
DILI	drug induced liver injury
DMC	data monitoring committee
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
ELF	enhanced liver fibrosis
ET	early termination
EOT	end of treatment
FAS	Full Analysis Set
FU	follow-up
GGT	uric acid Gamma-glutamyl transferase
GSI	Gilead Sciences, Inc.
HbA1c	hemoglobin A1c
HCV	hepatitis C virus
HDL	high-density lipoprotein
HDL-C	HDL-cholesterol
HLT	high level term
HLGT	high level group term
HOMA-IR	homeostasis model assessment of insulin resistance
ID	identification
IND	Investigational New Drug (Application)

INR	international normalized ratio
IXRS	interactive voice/web response system
LDH	lactate dehydrogenase
LDL-C	low-density lipoprotein cholesterol
LLT	lower level term
LLOQ	lower limit of quantitation
MedDRA	medical dictionary for regulatory activities
MRE	magnetic resonance elastography
MRI-PDFF	magnetic resonance imaging – proton density fat fraction
NASH	nonalcoholic steatohepatitis
PE	physical examination
PK	pharmacokinetic
PT	preferred term
Q1	first quartile
Q3	third quartile
QoL	quality of life
RBC	red blood cell
RNA	Ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SD	standard deviation
SOC	system organ class
TE	treatment-emergent
TFLs	tables, figures, and listings
ULN	upper limit of normal
ULOQ	upper limit of quantitation
VLDL-C	very low density lipoprotein-cholesterol
WBC	white blood cell
WHO	World Health Organization
WPAI	work productivity and activity impairment questionnaire

PHARMACOKINETIC ABBREVIATIONS

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

1. INTRODUCTION

This statistical analysis plan (SAP) describes the statistical analysis methods and data presentations to be used in tables, figures, and listings (TFLs) in the clinical study report (CSR) for Study GS-US-426-3989. This SAP is based on the study protocol Amendment 1.1 dated 19 December 2016 and the electronic case report form (eCRF). The SAP will be finalized before database finalization. Any changes made after the finalization of the SAP will be documented in the CSR.

1.1. Study Objectives

The primary objective of this study is as follows:

- To evaluate the safety and tolerability of GS-0976 in subjects with nonalcoholic steatohepatitis (NASH).

The exploratory objectives of this study are as follows:

1.2. Study Design

1.2.1. Design Configuration, Subject Population and Treatment Groups

This is a Phase 2, randomized, double-blind, placebo-controlled study designed to evaluate the safety, tolerability, and efficacy of GS-0976 in subjects with NASH. To be eligible to participate, subjects must have evidence of hepatic steatosis and increased liver stiffness as assessed by MRI-PDFF and MRE, respectively, or a historical liver biopsy consistent with NASH and noncirrhotic fibrosis. Any subject with history of decompensated liver disease, including ascites, hepatic encephalopathy, or variceal bleeding, will be ineligible.

Subjects meeting the study's entry criteria will be randomly assigned in a 2:2:1 ratio to 1 of 3 different treatment groups, A, B, and C, respectively:

- Group A (n = 50): GS-0976 5 mg (1 × 5 mg + PTM 5 mg + 2 × PTM 10 mg), orally once daily;
- Group B (n = 50): GS-0976 20 mg (2 × 10 mg + 2 × PTM 5 mg), orally once daily;
- Group C (n = 25): GS-0976 Placebo (2 × PTM 5 mg + 2 × PTM 10 mg), orally once daily.

Randomization will be stratified by the presence or absence of diabetes mellitus as determined by medical history, or based on Screening or Baseline/Day 1 lab values prior to first dosing if previously undiagnosed (ie, hemoglobin A1c ≥ 6.5% or fasting glucose ≥ 126 mg/dL).

1.2.2. Study Duration

The total time to complete all study visits is up to approximately 22 weeks including the following periods:

- 6-week screening period
- 12-week treatment period
- 4-week follow-up period

1.2.3. Schedule of Assessments

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

1.3. Sample Size and Power

Due to the exploratory nature of this study, no formal power calculations were used to determine sample size. The number of subjects was chosen based on clinical experience with other similar proof-of-concept studies. However, assuming that 4% of subjects in the Placebo arm (N = 25) and 32% in the GS-0976 20 mg arm (N = 50) have a ≥ 30% reduction in MRI-PDFF at Week 12, this sample size will provide 80% power to detect the difference between GS-0976 and Placebo based on a 2-sided Fisher's exact test at a significance level of 0.05.

2. TYPE OF PLANNED ANALYSIS

2.1. Interim Analyses

2.1.1. Data Monitoring Committee Analyses

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

The first DMC review will be conducted after approximately 20 subjects have been enrolled and every 3 to 4 months thereafter to monitor the study for safety events until all randomized subjects complete or discontinue the study. The DMC will meet on an ad hoc basis if there are at least 3 Grade 3 or higher serious, treatment-related adverse events (AEs) observed in the study, based on the Common Terminology Criteria for Adverse Events (CTCAE). In the event of two similar Grade 4-CTCAE treatment-related adverse events or one Grade 5-CTCAE treatment-related adverse event, the DMC will review the data and advise regarding stopping or continuing the study.

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

2.1.2. Interim Analysis

There is no interim analysis planned for this study.

2.2. Final Analysis

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

3. GENERAL CONSIDERATIONS FOR DATA ANALYSES

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

Data collected in the study will be presented in by subject listings for all subjects in the specified analysis set and will be sorted by subject ID number, visit date, and time (if applicable), unless otherwise specified. Data collected on log forms, such as AEs, will be presented in chronological order for each subject.

3.1. Analysis Sets

Analysis sets define the subjects to be included in an analysis. Analysis sets and their definitions are provided in this section. The analysis set will be identified and included as a subtitle of each table, figure, and listing.

For each analysis set, the number and percentage of subjects eligible for inclusion, as well as the number and percentage of subjects who were excluded and the reasons for their exclusion, will be summarized. Percentage will be calculated in proportion to the number of subjects in the all randomized analysis set by treatment group.

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

3.1.1. All Randomized Analysis Set

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

3.1.2. Full Analysis Set

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

3.1.3. Safety Analysis Set

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

3.1.4. Pharmacokinetic Analysis Set

The Pharmacokinetic (PK) Analysis Set will include all randomized subjects who took at least 1 dose of study drug and have at least 1 nonmissing postdose concentration value reported by the PK laboratory.

This is the primary analysis set for all PK analyses.

3.1.5. CCI [redacted]

[redacted]

3.2. Subject Grouping

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

Treatment groups GS-0976 20 mg and GS-0976 5 mg will be combined together as group GS-0976 pooled for analysis based on Safety Analysis Set. The summary will be prepared by treatment groups in the order of GS-0976 20 mg, GS-0976 5 mg, GS-0976 pooled, and Placebo.

3.3. Strata and Covariates

Subjects will be randomly assigned to treatment groups via the interactive web response system (IXRS) in a 2:2:1 ratio using a stratified randomization schedule. Stratification will be based on the presence or absence of diabetes mellitus.

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

3.4. Examination of Subject Subgroups

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

- presence of diabetes mellitus
- absence of diabetes mellitus

3.5. Multiple Comparisons

Adjustments for multiplicity will not be made because no formal statistical testing will be performed in this study. Any p-values displayed are for exploratory purposes only.

3.6. Missing Data and Outliers

3.6.1. Missing Data

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

For missing MRI-PDFF, imputation rules are specified in Section 6.2.3. For missing last dosing date of study drug, imputation rules are described in Section 4.2.1. The handling of missing or incomplete dates for AE onset is described in Section 7.1.5.2, and for prior and concomitant medications in Section 7.4.

3.6.2. Outliers

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

3.7. Data Handling Conventions and Transformations

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

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

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

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

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

If methods based on the assumption that the data are normally distributed are not adequate, analyses may be performed on transformed data or nonparametric analysis methods may be used, as appropriate.

Natural logarithm-transformation will be used for blood concentrations and analysis of PK parameters. Plasma concentration values that are below the limit of quantitation (BLQ) will be presented as "BLQ" in the concentration data listing. Values that are BLQ will be treated as 0 at predose time points, and one-half the value of the LLOQ at postbaseline time points.

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

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

3.8. Analysis Visit Windows

3.8.1. Definition of Study Day

Study day is the day relative to the date of the first dose of study drug. Study Day 1 will be defined as the day of first dose of study drug administration.

Study day will be calculated from the date of first dose of study drug administration 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

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

3.8.2. Definition Analysis Visit Windows

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

In general, the baseline value will be the last nonmissing value on or prior to the first dosing date of study drug. For imaging the data, baseline will be the first nonmissing value from screening up to first dosing date plus 4 weeks.

Selected safety and efficacy data collected up to and including the last dosing date plus 30 days (or 42 days for imaging data) will be mapped according to the following analysis windows. Early termination (ET) or follow-up (FU) will use the nominal visit name.

Table 3-1. Analysis Visit Windows for Vital Signs Including Weight, Chemistry, Hematology, Coagulation Labs, Lipid Profile, and Pooled Cohort Score and Risk

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

NA = not applicable

Table 3-2. Analysis Visit Windows for FibroSure/FibroTest, CK-18, ELF (and its components), Free Fatty Acid, C-Reactive Protein, ApoA1, ApoB, and Bile Acids

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

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

Analysis Visit	Study Day	Lower Limit	Upper Limit
Baseline/Day	1	NA	1
Week 4	29	2	56
Week 12	85	57	> 85

Table 3-4. Analysis Visit Windows for Waist Circumference, ECG, HbA1c, and QoL-Questionnaire

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

Table 3-5. Analysis Visit Windows for FibroScan, MRE, and MRI-PDFF

Analysis Visit	Study Day	Lower Limit	Upper Limit
Baseline/Day	1	NA	29
Week 12	85	30	> 85

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

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

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

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

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

- In general, the baseline value will be the last nonmissing value on or prior to the first dosing date of study drug, unless specified differently. If multiple measurements occur on the same day, the last nonmissing value prior to the time of first dosing of study drug will be considered as the baseline value. If these multiple measurements occur at the same time or the time is not available, the average of these measurements (for continuous data) will be considered the baseline value.

- For postbaseline values:
- The record closest to the nominal day (the nominal day for Week x is Day 7x + 1) for that visit will be selected.
- If there are 2 records that are equidistant from the nominal day, the later record will be selected.
- If there is more than 1 record on the selected day, the average will be taken, unless otherwise specified.

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

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

4. SUBJECT DISPOSITION

4.1. Subject Enrollment and Disposition

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

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

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

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

- Safety Analysis Set
- Full Analysis Set
- PK Analysis Set
- CCI [redacted]
- Completed study drug
- Did not complete study drug, with reasons for premature discontinuation of study drug
- Completed study
- Did not complete the study, with reasons for premature discontinuation of study

In addition, a flowchart will be provided to depict the disposition.

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

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

4.2. Extent of Study Drug Exposure and Adherence

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

4.2.1. Duration of Exposure to Study Drug

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

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

The total duration of exposure to study drug will be summarized using descriptive statistics (sample size, mean, SD, median, Q1, Q3, minimum, and maximum) and using the number (ie, cumulative counts) and percentage of subjects exposed through the following time points: 1 day, 1 week, 4 weeks, 8 weeks, and 12 weeks.

Summaries will be provided by treatment group for the Safety Analysis Set.

No formal statistical testing is planned.

4.2.2. Adherence to Study Drug

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

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

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

4.2.2.1. Prescribed Adherence

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

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

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

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

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

No formal statistical testing is planned.

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

4.3. Protocol Deviations

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

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

5. BASELINE CHARACTERISTICS

5.1. Demographics

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

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

5.2. Other Baseline Characteristics

Other baseline characteristics include:

- body weight (in kg)
- height (in cm)
- body mass index as a continuous variable and as categories (< 18.5 kg/m^2, 18.5 to < 25 kg/m^2, 25 to < 30 kg/m^2, and ≥ 30 kg/m^2)
- diabetes mellitus (diabetic or nondiabetic)
- MRI-PDFF
- MRE
- FibroScan (if available)
- FibroSURE/FibroTest
- ELF test
- ALP
- ALT
- AST
- direct and total bilirubin
- GGT

- estimated glomerular filtration rate (eGFR) (Cockcroft-Gault)
- homeostasis model assessment of insulin resistance (HOMA-IR)
- fasting glucose
- fasting insulin
- international normalized ratio (INR)
- hemoglobin A1c (HbA1c)
- total cholesterol
- triglycerides
- high-density lipoprotein cholesterol (HDL-C)
- calculated low-density lipoprotein cholesterol (LDL-C)
- calculated Non-HDL-C
- calculated Very Low Density Lipoprotein cholesterol (VLDL-C)
- free fatty acid
- C-reactive protein (CRP)
- Total bile acids
- waist circumference
- systolic blood pressure treated status (treated/not treated)
- smoking status

These baseline characteristics will be summarized by treatment group and overall using descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum) for continuous variables and using number and percentage of subjects for categorical variables. The summary of baseline characteristics will be provided for the Safety Analysis Set. No formal statistical testing is planned.

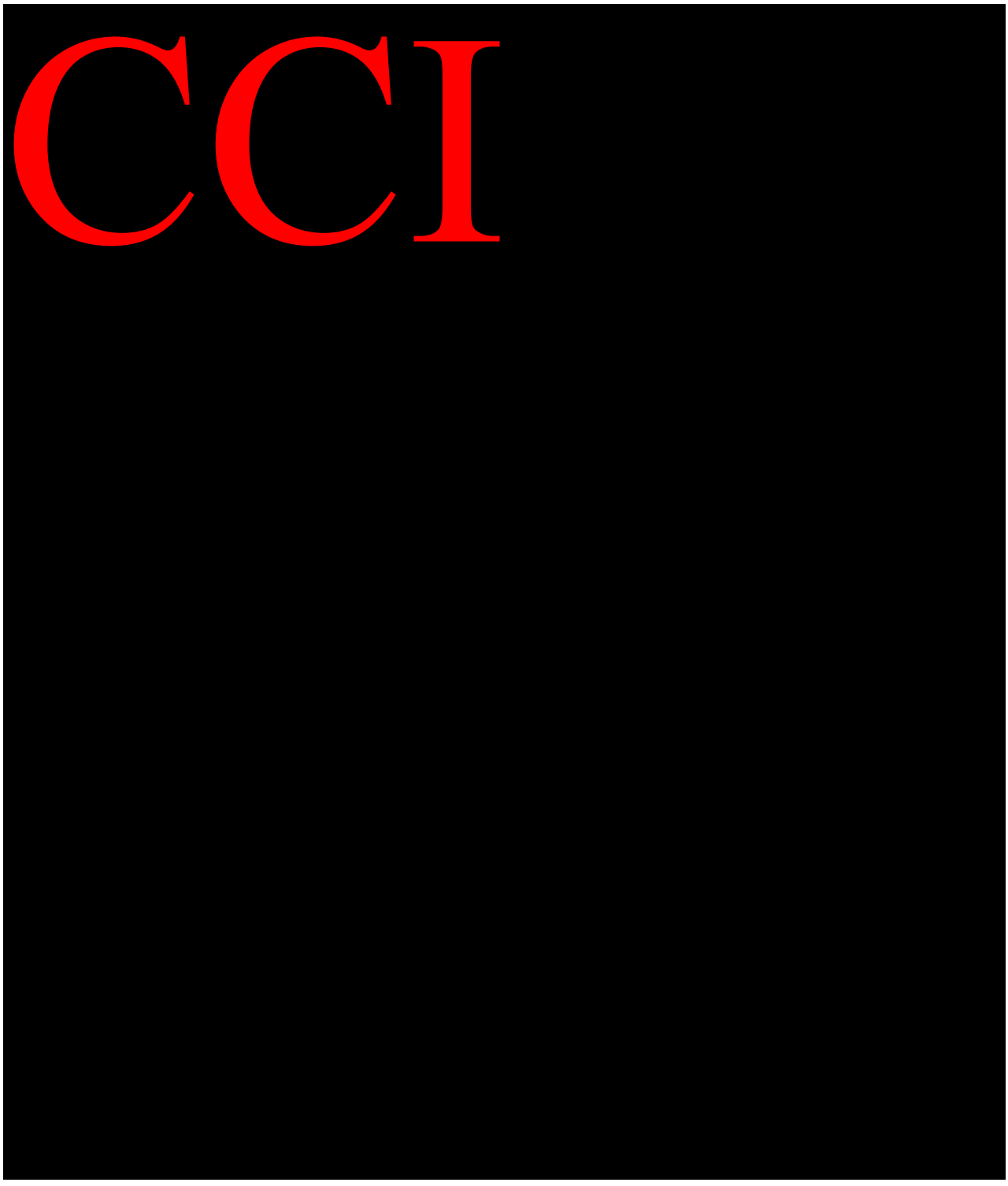
A by-subject listing of then Other Baseline Characteristics will be provided by subject ID number in ascending order.

5.3. Medical History

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

6. EFFICACY ANALYSES

6.1. Exploratory Efficacy Endpoints



[redacted]

6.1.1. [redacted]

[redacted]

[redacted]

6.2. Analysis Methods for Exploratory Efficacy Endpoints

6.2.1. Statistical Analysis Models

CCI

[redacted]

6.2.2. Statistical Analysis Methods

For exploratory efficacy endpoints, the number and percentage of subjects in each category will be presented for categorical variables. Descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum) will be provided for continuous exploratory efficacy variables by treatment group, as follows:

- Baseline values
- Values at each postbaseline visit
- Change from baseline at each postbaseline visit
- Percent change from baseline at each postbaseline (except for pooled cohort risk score)

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

For continuous exploratory efficacy endpoints, mean (SD) of the observed change from baseline values will be plotted using a line plot by treatment group and visit.

Listings of all exploratory efficacy endpoints will be provided.

6.2.3. Missing MRI-PDFF Data Handling

For MRI-PDFF data, the first analyzable value from multiple echo (ME) series at each time point will be used. The mean of all analyzable segments by time point reported will be used. If there are subjects missing ME series results but have double double echo (DDE) series results, 95% CI based on t statistics will be calculated for the mean difference in ME and DDE series results. If the 95% CI is within [−3%, 3%], then the DDE values (mean of analyzable segments reported) will be used to impute for missing ME results. If a subject has both (baseline and Week 12) DDE series values available, and at least 1 ME series value requires imputation, then the corresponding DDE series result will be used for both visits.

6.2.4. Imaging Data Repeat Scan and Re-read

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

6.3. Subgroup Analysis of the Efficacy Endpoints

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

- presence of diabetes mellitus
- absence of diabetes mellitus

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

For each subgroup, the proportion of subjects with at least 30% reduction in MRI-PDFF at Week 12 and the proportion of subjects with at least 15% reduction in MRE at Week 12 will be reported for each treatment group by using a point estimate and 95% CI of the proportion

based on the Clopper-Pearson method. The 95% CI for the difference in proportion between GS-0976 and Placebo will also be provided.

Within each subgroup, the change from baseline of MRI-PDFF and MRE at Week 12 will be analyzed by using an ANCOVA model, with treatment group, and baseline MRI-PDFF or MRE as covariates. For change from baseline, LS means and 95% CIs of LS means will be reported for each treatment group. For treatment differences (GS-0976 – Placebo) of changes from baseline of MRI-PDFF or MRE at Week 12, LS means and 95% CIs will be reported.

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

6.4. Changes From Protocol-Specified Efficacy Analyses

There is no change from protocol specified analysis.

7. SAFETY ANALYSES

7.1. Adverse Events and Deaths

7.1.1. Adverse Event Dictionary

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

7.1.2. Adverse Event Severity

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

7.1.3. Relationship of Adverse Events to Study Drug

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

7.1.4. Serious Adverse Events

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

7.1.5. Treatment-Emergent Adverse Events

7.1.5.1. Definition of Treatment-Emergent Adverse Events

Treatment-emergent adverse events (TEAEs) are defined as 1 or both of the following:

- Any AEs with an onset date on or after the study drug start date and no later than 30 days after permanent discontinuation of study drug
- Any AEs leading to premature discontinuation of study drug.

7.1.5.2. Incomplete Dates

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

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

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

7.1.6. Summaries of Adverse Events and Deaths

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

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

- TEAEs of Grade 3 or higher (by maximum severity)
- TEAEs of Grade 2 or higher
- All TE treatment-related AEs
- TE treatment-related AEs of Grade 3 or higher (by maximum severity)
- TE treatment-related AEs of Grade 2 or higher
- All TE SAEs
- All TE treatment-related SAEs
- All TEAEs leading to premature discontinuation of study drug
- All TEAEs leading to premature discontinuation of study
- All TEAEs leading to dose temporary interruption of study drug

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

Multiple events will be counted only once per subject in each summary. Adverse events will be summarized and listed first in alphabetic order of SOC and HLT within each SOC (if applicable), and then by PT in descending order of GS-0976 20 mg frequency within each SOC (HLT, if present). For summaries by severity grade, the most severe grade will be used for those AEs that occurred more than once in an individual subject during the study.

In addition to the above summary tables, TEAEs and TE treatment-related AEs will be summarized by PT only for the following, in descending order of GS-0976 20 mg frequencies:

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

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

- All AEs, indicating whether the event is treatment emergent
- All AEs of Grade 3 or higher
- All AEs of Grade 2 or higher
- SAEs

- Deaths
- AEs leading to premature discontinuation of study drug
- AEs leading to premature discontinuation of study
- AEs leading to temporary interruption of study drug

7.2. Laboratory Evaluations

Laboratory data collected during the study will be analyzed and summarized using both quantitative and qualitative methods. The analysis will be based on values reported in conventional units. When values are below the LOQ, they will be listed as such, and the closest imputed value will be used for the purpose of calculating summary statistics as specified in Section 3.7.

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

No formal statistical testing is planned.

7.2.1. Summaries of Numeric Laboratory Results

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

- Chemistry Panel:

  Creatinine, fasting glucose, fasting insulin, eGFR using the Cockcroft-Gault equation, serum creatinine

- Coagulation Panel: INR
- Hematology: white blood cell (WBC), neutrophils, lymphocytes, hemoglobin, platelets

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

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

Change from baseline to a postbaseline visit will be defined as the postbaseline value minus the baseline value. The mean, median, Q1, Q3, minimum, and maximum values will be displayed to the reported number of digits; SD values will be displayed to the reported number of digits plus 1.

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

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

7.2.2. Graded Laboratory Values

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

7.2.2.1. Treatment-Emergent Laboratory Abnormalities

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

7.2.2.2. Treatment-Emergent Marked Laboratory Abnormalities

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

7.2.2.3. Summaries of Laboratory Abnormalities

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

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

- Graded laboratory abnormalities

- Grade 3 or 4 laboratory abnormalities
- Marked laboratory abnormalities

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

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

7.2.3. Liver-related Laboratory Evaluations

Liver-related abnormalities after initial study drug dosing will be examined and summarized using the number and percentage of subjects who were reported to have the following laboratory test values listed in Section 7.2.3.1 for postbaseline measurements:

The summary will include data from all postbaseline visits up to 30 days after the last dose of study drug. For individual laboratory tests, subjects will be counted once based on the most severe postbaseline values. For both the composite endpoint of AST or ALT and total bilirubin, ALP, INR (as described below), subjects will be counted once when the criteria are met at the same postbaseline visit date. The denominator is the number of subjects in each reporting group (if applicable) in the Safety Analysis Set who have nonmissing postbaseline values of all relevant tests at the same postbaseline visit date.

7.2.3.1. Criteria for Observation of Drug Induced Liver Injury (DILI)

For subjects with ALT (AST) baseline meeting one of the following 2 categories, close observation for DILI should be considered if the subjects meet any of the postbaseline criteria corresponding to each baseline category below.

1) For subjects with ALT (AST) below ULN at study baseline AND

- meeting any of the following postbaseline criteria for liver-related events:
  - ALT (AST) > 3 × ULN at any time
  - Total Bilirubin > 2 × ULN
  - ALP > 3 × ULN
  - INR > 1.5 (except for subjects on anticoagulant therapy)
- meeting any of the following postbaseline criteria for drug withheld:
  - ALT (AST) > 3 × ULN and Total Bilirubin > 2 × ULN

— ALT (AST) > 3 × ULN and INR > 1.5 (except for subjects on anticoagulant therapy)

— ALT (AST) > 5 × ULN

— ALT (AST) > 8 × ULN

2) For subjects with ALT (AST) greater than or equal to 1 × ULN at study baseline AND

- meeting any of the following postbaseline criteria for liver-related events :

  — ALT (AST) > 2 × Baseline at any time

  — Total Bilirubin > 2 × ULN

  — ALP > 3 × ULN

  — INR > 1.5 (except for subjects on anticoagulant therapy)

- Meeting any of the following postbaseline criteria for drug withheld:

  — ALT (AST) > 3 × ULN and Total Bilirubin > 2 × ULN

  — ALT (AST) > 3 × ULN and INR > 1.5 (except for subjects on anticoagulant therapy)

  — ALT (AST) > 5 × ULN

  — ALT (AST) > 8 × ULN

7.2.3.2. Summaries of Criteria for Observation of DILI

The subjects who meet the criteria for close observation of DILI described in Section 7.2.3.1 will be summarized (by using number and percentage of subjects) by treatment, ALT (AST) baseline condition (whether below ULN, or greater than or equal to 1 × ULN), and corresponding postbaseline criteria listed in Section 7.2.3.1.

A listing will be provided for the subjects who met at least 1 of the above criteria.

7.3. Body Weight, Waist Circumference and Vital Signs

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

- Baseline value

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

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

Median (Q1, Q3) of the observed change from baseline values for body weight and waist circumference will be plotted by treatment group and visit. In the case of multiple values in an analysis window, data will be selected for analysis as described in Section 3.8.3. No formal statistical testing is planned.

A by-subject listing of vital signs will be provided by subject ID number and visit in chronological order. In the same manner, a by-subject listing of body weight, height, and BMI will be provided.

7.4. Prior and Concomitant Medications

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

7.4.1. Prior Medications

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

Prior medications will be summarized by Anatomical Therapeutic Chemical (ATC) drug class Level 4 and preferred name using the number and percentage of subjects for each treatment group and overall. A subject reporting the same medication more than once will be counted only once when calculating the number and percentage of subjects who received that medication. The summary will be ordered alphabetically by ATC medical class and then by preferred term in order of descending overall frequency within each ATC medical class. For drugs with the same frequency, sorting will be done alphabetically.

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

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

7.4.2. Concomitant Medications

Concomitant medications are defined as medications taken while a subject took study drug. Use of concomitant medications will be summarized by Anatomical Therapeutic Chemical (ATC) drug class Level 4 and preferred name using the number and percentage of subjects for each treatment group. A subject reporting the same medication more than once will be counted only once when calculating the number and percentage of subjects who received that medication. The summary will be ordered alphabetically by ATC medical class and then by preferred term in descending overall frequency within each ATC medical class. For drugs with the same frequency, sorting will be done alphabetically.

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

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

7.5. Electrocardiogram Results

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

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

7.6. Other Safety Measures

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

7.7. Changes From Protocol-Specified Safety Analyses

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

8. PHARMACOKINETIC ANALYSES

8.1. PK Sample Collection

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

CCI [redacted]

8.2. PK Analyses Related to Intensive PK Sampling

CCI [redacted]. Concentrations of GS-0976 and its metabolites in plasma will be determined using validated bioanalytical assays.

8.2.1. Estimation of PK Parameters

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

All predose sample times before time zero will be converted to 0.

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

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

8.2.2. PK Parameters

Pharmacokinetic parameters will be generated for all subjects in the PK Substudy Analysis Set. For each subject, the following PK parameters will be calculated for GS-0976 and its metabolites as appropriate to evaluate the PK objectives of the study.

Table 8-1. Study Treatments and Associated Analytes

Treatment	Analyte
GS-0976 20 mg tablet	GS-0976, GS-834773, and others as appropriate
GS-0976 5 mg tablet	GS-0976, GS-834773, and others as appropriate

Table 8-2. PK Parameters for Each Analyte

Analyte	Parameters
GS-0976	AUC_{last}, AUC_{tau}, C_{max}, T_{max}, C_{last}, T_{last}, C_{tau}, λz, CLss/F, and $t_{1/2}$
GS-834773	AUC_{last}, AUC_{tau}, C_{max}, T_{max}, C_{last}, T_{last}, C_{tau}, λz, and $t_{1/2}$

Individual subject concentration data and individual subject PK parameters for GS-0976 and its metabolites will be listed and summarized using descriptive statistics by treatment. Summary statistics (n, mean, SD, coefficient of variation [%CV], median, min, max, Q1, and Q3) will be presented for both individual subject concentration data and individual subject PK parameters by time point and by treatment. Moreover, the geometric mean, 95% CI, and the mean and SD of the natural log-transformed values will be presented for individual subject PK parameter data.

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

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

The following tables will be provided for each analyte by treatment for the PK Substudy:

CCI

CCI [redacted]

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

The following listings will be provided:

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

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

9. REFERENCES

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

Koch GG, Carr GJ, Amara IA, Stokes ME, Uryniak TJ. Categorical Data Analysis. Chapter 13 in Berry, D.A. (ed.). Statistical Methodology in the Pharmaceutical Sciences. New York: Marcel Dekker, Inc., 1989:pp. 414-21.

10. SOFTWARE

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

11. SAP REVISION

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

12. APPENDIX

Appendix 1. Procedures Table for Study GS-US-426-3989

Assessments	Screening[a]	Baseline / Day 1	On-treatment Visits				Follow-Up Visit[b] (± 5 Days)
			Week 1 ± 3 days	Week 4 ± 3 days	Week 8 ± 3 days	Week 12/ET[b] ± 7 days	
Clinical Assessments							
Written Informed Consent[c]	X						
Determine Eligibility	X	X					
Medical History	X						
Physical Examination	X	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]
Vital Signs[e] including Weight	X	X	X	X	X	X	X
Height	X						
Waist Circumference		X				X	
12- lead ECG	X	X				X	
Ultrasound[f]	X						
MRE, MRI-PDFF	X					X	
FibroScan®[g]		X				X	
SF-36, WPAI, and CLDQ Questionnaires[h]		X				X	
Adverse Events	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X
Dispense Study Drugs		X		X	X		
Review of Study Drug Dosing Compliance (Pill Count)			X	X	X	X	
Laboratory Assessments							
Subject Fasting[i]	X	X	X	X	X	X	X

Assessments	Screening[a]	Baseline / Day 1	On-treatment Visits				Follow-Up Visit[b] (± 5 Days)
			Week 1 ± 3 days	Week 4 ± 3 days	Week 8 ± 3 days	Week 12/ET[b] ± 7 days	
Chemistry, Hematology, Coagulation Panel	X	X	X	X	X	X	X
Lipid Profile		X	X	X	X	X	X
Pregnancy Test[j]	X	X		X	X	X	X
Serum FSH[k]	X						
Single PK Sampling			X	X	X	X	
Hemoglobin A1c	X	X				X	
Blood and Urine Collection (Biomarker)		X	X	X		X	
Stool Collection (Biomarker)		X				X	
Urine Drug Screening[l]	X						
HIV-1, HBV & HCV[m] Serology	X						
CCI							
Genomic Sample[n]		X					

a Screening assessments to be completed within 4 weeks prior to Day 1. The Screening period also may be extended longer under special circumstances with the explicit approval of the Gilead Medical Monitor.
b Subjects discontinuing treatment at any time for any reason (Early Termination – ET) should complete the procedures listed for the Week 12/ET visit AND the Follow-Up visit.
c Obtain written informed consent before initiation of any screening procedure.
d Symptom-driven physical examination
e Vital signs include blood pressure, heart rate, respiration rate, and body temperature.
f Ultrasound may be performed if necessary to confirm NAFLD.
g Perform FibroScan® if available.
h It is recommended that QoL questionnaires be completed prior to any study procedures being performed and prior to the subject seeing a health care provider. Refer to the Study Reference Binder for guidance on QoL questionnaire administration for subjects with QoL questionnaires available at Baseline/Day 1.
i Subjects must be in a fasted state at least 8 hours prior to blood collection.
j Females of childbearing potential only (See Appendix 3 in protocol). Serum pregnancy test at Screening and urine pregnancy test at all other visits, except Week 1.
k CCI
l Drug screen for amphetamines, cocaine, and opiates (i.e., heroin, morphine).
m HCV Ab positive, reflex to HCV RNA.
n CCI

Appendix 2. Pooled Cohort Risk Score and Pooled Cohort Risk Calculation

No.	Parameters	Coefficient			
		Female		Male	
		White or Other	African America	White or Other	African America
1	Ln Age (y)	–29.799	17.114	12.344	2.469
2	Ln Age, Squared	4.884	N/A	N/A	N/A
3	Ln Total Cholesterol (mg/dL)	13.540	0.940	11.853	0.302
4	Ln Age × Ln Total Cholesterol	–3.114	N/A	–2.664	N/A
5	Ln HDL-C (mg/dL)	–13.578	–18.920	–7.990	–0.307
6	Ln Age × Ln HDL-C	3.149	4.475	1.769	N/A
7	Ln Treated Systolic BP (mm Hg)	2.019	29.291	1.797	1.916
8	Ln Age × Ln Treated Systolic BP	N/A	–6.432	N/A	N/A
9	Ln Untreated Systolic BP (mm Hg)	1.957	27.820	1.764	1.809
10	Ln Age × Ln Untreated Systolic BP	N/A	–6.087	N/A	N/A
11	Current Smoker (1=Yes, 0=No)	7.574	0.691	7.837	0.549
12	Ln Age × Current Smoker	–1.665	N/A	–1.795	N/A
13	Diabetes (1=Yes, 0=No)	0.661	0.874	0.658	0.645

A	Baseline Survival	0.9665	0.9533	0.9144	0.8954
B	Individual Sum = ∑(coefficient*parameter)	For each individual patient, individual sum is summation of product of each parameter and its corresponding coefficient for that sex-race group for all parameters listed above (#1 -#13). Note: N/A indicates that the specific coefficient is not available thus the corresponding parameter will not be included in calculation.			
C	Group Wise Mean Sum of (Coefficient × parameter)	Equal to the [sum of individual sum of all patients in sex- and race- specific group] divided by the [total number of patients in that sex- and race- specific group].			
		–29.18	86.61	61.18	19.54
D	**Pooled Cohort Risk Score**	= B – C = Individual Sum - Group Wise Mean Sum of (Coefficient × parameter)			
E	**Pooled Cohort Risk** =Estimated probability of a first hard ASCVD event within 10 years *	= **1 - A^exp(B-C)** = 1 - Baseline Survival ^ exp (Individual Sum- Group wise mean sum)			

* ASCVD = atherosclerotic cardiovascular disease; BP = blood pressure; HDL-C = high-density lipoprotein cholesterol; Ln = natural logarithm. Age is the actual age when the lab parameters are collected for the visit.. Total Cholesterol and HDL-C, Systolic BP are assessed at visit when risk score are collected. Smoker, Diabetes and status of hypertension treatment are collected at Screening/Baseline. Round Pooled Cohort Risk Score to 0.001. The lab parameters need to be measured from the same blood draw.

Appendix 3. Health Related QoL Score Calculation:

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

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

- **CLDQ (Chronic Liver Disease Questionnaire):**

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

Abdominal (AB) = Mean of {R1, R5, R17}

Fatigue (FA) = Mean of {R2, R4, R8, R11, R13, R35}

Systemic (SY) = Mean of {R3, R6, R21, R23, R27, R36}

Activity (AC) = Mean of {R7, R9, R14, R30, R31}

Emotion (EM) = Mean of {R10, R12, R15, R16, R19, R20, R24, R26, R34}

Worry (WO) = Mean of {R18, R22, R25, R28, R29, R32, R33}

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

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

- **WPAI (Work Productivity and Activity Impairment): SHP**

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

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

Percent work time missed (Absenteeism) = 100 × Q2 / (Q2 + Q4)

Percent impairment while working (Presenteesism) = 100 × Q5 / 10

Percent overall work productivity loss =

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

Question 6 is applicable to all subjects:

Percent activity impairment = 100 × Q6 / 10.

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

Appendix 4. CTCAE Grade for Laboratory Parameters

CTCAE v4.03	CTCAE Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Anemia	Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated	Life-threatening consequences; urgent intervention indicated	Death
Hypoalbuminemia	<LLN - 3 g/dL; <LLN - 30 g/L	<3 - 2 g/dL; <30 - 20 g/L	<2 g/dL; <20 g/L	Life-threatening consequences; urgent intervention indicated	Death
Alkaline phosphatase increased	>ULN – 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN	-
Alanine aminotransferase (ALT) increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN	-
Activated partial thromboplastin time (APTT) prolonged	>ULN - 1.5 x ULN	>1.5 - 2.5 x ULN	>2.5 x ULN; hemorrhage	-	-
Aspartate aminotransferase (AST) increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN	-
Blood bilirubin increased	>ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 - 10.0 x ULN	>10.0 x ULN	-
Hypercalcemia	Corrected serum calcium of >ULN - 11.5 mg/dL; >ULN - 2.9mmol/L; Ionized calcium >ULN- 1.5 mmol/L	Corrected serum calcium of>11.5 - 12.5 mg/dL; >2.9 - 3.1 mmol/L; Ionized calcium >1.5 -1.6 mmol/L; symptomatic	Corrected serum calcium of >12.5 - 13.5 mg/dL; >3.1 - 3.4 mmol/L; Ionized calcium >1.6 - 1.8 mmol/L; hospitalization indicated	Corrected serum calcium of >13.5 mg/dL; >3.4 mmol/L; Ionized calcium >1.8 mmol/L; life-threatening consequences	Death
Hypocalcemia	Corrected serum calcium of <LLN - 8.0 mg/dL; <LLN - 2.0 mmol/L; Ionized calcium <LLN - 1.0 mmol/L	Corrected serum calcium of <8.0 - 7.0 mg/dL; <2.0 - 1.75 mmol/L; Ionized calcium <1.0 - 0.9 mmol/L; symptomatic	Corrected serum calcium of <7.0 - 6.0 mg/dL; <1.75 - 1.5 mmol/L; Ionized calcium <0.9 - 0.8 mmol/L; hospitalization indicated	Corrected serum calcium of <6.0 mg/dL; <1.5 mmol/L; Ionized calcium <0.8 mmol/L; life-threatening consequences	Death

CTCAE v4.03	CTCAE Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Chronic kidney disease	eGFR (estimated Glomerular Filtration Rate) or CrCl (creatinine clearance) <LLN – 60 ml/min/1.73 m2 or proteinuria 2+ present; urine protein/creatinine >0.5	eGFR or CrCl 59 – 30 ml/min/1.73 m2	eGFR or CrCl 29 – 15 ml/min/1.73 m2	eGFR or CrCl <15 ml/min/1.73 m2; dialysis or renal transplant indicated	Death
Creatinine increased	>1 - 1.5 x baseline; >ULN - 1.5 x ULN	>1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	>3.0 baseline; >3.0 - 6.0 x ULN	>6.0 x ULN	-
Gamma-glutamyl transferase (GGT) increased	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN	-
Hyperglycemia	Fasting glucose value >ULN - 160 mg/dL; Fasting glucose value >ULN - 8.9 mmol/L	Fasting glucose value >160 - 250 mg/dL; Fasting glucose value >8.9 - 13.9 mmol/L	>250 - 500 mg/dL; >13.9 - 27.8 mmol/L; hospitalization indicated	>500 mg/dL; >27.8 mmol/L; lifethreatening consequences	Death
Hypoglycemia	<LLN - 55 mg/dL; <LLN - 3.0 mmol/L	<55 - 40 mg/dL; <3.0 - 2.2 mmol/L	<40 - 30 mg/dL; <2.2 - 1.7 mmol/L	<30 mg/dL; <1.7 mmol/L; lifethreatening consequences; seizures	Death
Hemoglobin increased	Increase in >0 - 2 gm/dL above ULN or above baseline if baseline is above ULN	Increase in >2 - 4 gm/dL above ULN or above baseline if baseline is above ULN	Increase in >4 gm/dL above ULN or above baseline if baseline is above ULN	-	-
International normalized ratio (INR) increased	>1 - 1.5 x ULN; >1 - 1.5 times above baseline if on anticoagulation	>1.5 - 2.5 x ULN; >1.5 - 2.5 times above baseline if on anticoagulation	>2.5 x ULN; >2.5 times above baseline if on anticoagulation	-	-
Hyperkalemia	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L	>6.0 - 7.0 mmol/L; hospitalization indicated	>7.0 mmol/L; life-threatening consequences	Death
Hypokalemia	<LLN - 3.0 mmol/L	<LLN - 3.0 mmol/L; symptomatic; intervention Indicated	<3.0 - 2.5 mmol/L; hospitalization indicated	<2.5 mmol/L; life-threatening consequences	Death
Lymphocyte count decreased	<LLN - 800/mm3; <LLN - 0.8 x 10e9 /L	<800 - 500/mm3; <0.8 - 0.5 x 10e9 /L	<500 - 200/mm3; <0.5 - 0.2 x 10e9 /L	<200/mm3; <0.2 x 10e9 /L	-

CTCAE v4.03	CTCAE Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Lymphocyte count increased	-	>4000/mm3 - 20,000/mm3	>20,000/mm3	-	-
Hypermagnesemia	>ULN - 3.0 mg/dL; >ULN - 1.23 mmol/L	-	>3.0 - 8.0 mg/dL; >1.23 - 3.30 mmol/L	>8.0 mg/dL; >3.30 mmol/L; lifethreatening consequences	Death
Hypomagnesemia	<LLN - 1.2 mg/dL; <LLN - 0.5 mmol/L	<1.2 - 0.9 mg/dL; <0.5 - 0.4 mmol/L	<0.9 - 0.7 mg/dL; <0.4 - 0.3 mmol/L	<0.7 mg/dL; <0.3 mmol/L; lifethreatening consequences	Death
Neutrophil count decreased	<LLN - 1500/mm3; <LLN - 1.5 x 10e9 /L	<1500 - 1000/mm3; <1.5 - 1.0 x 10e9 /L	<1000 - 500/mm3; <1.0 - 0.5 x 10e9 /L	<500/mm3; <0.5 x 10e9 /L	-
Hypophosphatemia	<LLN - 2.5 mg/dL; <LLN - 0.8 mmol/L	<2.5 - 2.0 mg/dL; <0.8 - 0.6 mmol/L	<2.0 - 1.0 mg/dL; <0.6 - 0.3 mmol/L	<1.0 mg/dL; <0.3 mmol/L; lifethreatening consequences	Death
Platelet count decreased	<LLN - 75,000/mm3; <LLN - 75.0 x 10e9 /L	<75,000 - 50,000/mm3; <75.0 - 50.0 x 10e9 /L	<50,000 - 25,000/mm3; <50.0 - 25.0 x 10e9 /L	<25,000/mm3; <25.0 x 10e9 /L	-
Hypernatremia	>ULN - 150 mmol/L	>150 - 155 mmol/L	>155 - 160 mmol/L; hospitalization indicated	>160 mmol/L; life-threatening consequences	Death
Hyponatremia	<LLN - 130 mmol/L	-	<130 - 120 mmol/L	<120 mmol/L; life-threatening consequences	Death
Hyperuricemia	>ULN - 10 mg/dL (0.59 mmol/L) without physiologic consequences	-	>ULN - 10 mg/dL (0.59 mmol/L) with physiologic consequences	>10 mg/dL; >0.59 mmol/L; lifethreatening consequences	Death
White blood cell (WBC) decreased	<LLN - 3000/mm3; <LLN - 3.0 x 10e9 /L	<3000 - 2000/mm3; <3.0 - 2.0 x 10e9 /L	<2000 - 1000/mm3; <2.0 - 1.0 x 10e9 /L	<1000/mm3; <1.0 x 10e9 /L	-
Hypertriglyceridemia	150 mg/dL - 300 mg/dL; 1.71 mmol/L - 3.42 mmol/L	>300 mg/dL - 500 mg/dL; >3.42 mmol/L - 5.7 mmol/L	>500 mg/dL - 1000 mg/dL; >5.7 mmol/L - 11.4 mmol/L	>1000 mg/dL; >11.4 mmol/L; life-threatening consequences	Death
Cholesterol high	>ULN - 300 mg/dL; >ULN - 7.75 mmol/L	>300 - 400 mg/dL; >7.75 - 10.34 mmol/L	>400 - 500 mg/dL; >10.34 - 12.92 mmol/L	>500 mg/dL; >12.92 mmol/L	-

Note: Refer to Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03, which can be found at http://evs.nci nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (yyyy-MM-dd hh:mm)
PPD	Clinical eSigned	2017-07-28 09:22
PPD	Biostatistics eSigned	2017-07-28 17:38