STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 1 Open-Label Study to Evaluate the Pharmacokinetics of GS-9876 in Subjects with Impaired Renal Function
Study Phase:	1
Name of Test Drug:	GS-9876
Study Number:	GS-US-379-1932
Protocol Version (Date):	Original (10 October 2016) Amendment 1 (09 January 2017)
Analysis Type:	Final Analysis
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CONFIDENTIAL AND PROPRIETARY INFORMATION

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LIST OF ABBREVIATIONS

AE	adverse event
ANOVA	analysis of variance
AUC	area under the curve
BLQ	below the limit of quantitation
BMI	body mass index
CI	confidence interval
CLcr	creatinine clearance
CRF	case report form
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
ECG	Electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
ET	early termination
GLSM	geometric least squares mean
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
ID	Identification
LLOQ	lower limit of quantitation
LOQ	limit of quantitation
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
PD	Pharmacodynamics
PK	pharmacokinetic(s)
PT	prothrombin time
PT	preferred term
Q1	first quartile
Q3	third quartile
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SE	standard error
SOC	system organ class
WHO	World Health Organization

PHARMACOKINETIC ABBREVIATIONS AND DEFINITIONS

AUC_{last}	area under the plasma/serum concentration versus time curve from time zero to the last quantifiable concentration
AUC_{inf}	area under the plasma/serum concentration versus time curve extrapolated to infinite time, calculated as $AUC_{last} + (C_{last}/\lambda_z)$
$\%AUC_{exp}$	percentage of AUC extrapolated between AUC_{last} and AUC_{inf}
C_{max}	maximum observed plasma/serum concentration of drug
C_{last}	last observed quantifiable plasma/serum concentration of the drug
CL/F	apparent oral clearance after administration of the drug: $CL/F = Dose/AUC_{inf}$, where "Dose" is the dose of the drug
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
T_{max}	time (observed time point) of C_{max}
T_{last}	time (observed time point) of C_{last}
$t_{½}$	estimate of the terminal elimination half-life of the drug in plasma/serum, calculated by dividing the natural log of 2 by the terminal elimination rate constant (λ_z)
V_z/F	apparent volume of distribution of the drug
A_e	Amount of unchanged drug excreted in urine calculated either over a specific interval ($A_{e(interval)}$) or cumulatively over all collection intervals, calculated as (Concentration of unchanged drug in urine) · (Volume of urine collected)
CL_r	The renal clearance of unchanged drug in a specific interval ($CL_{r(interval)}$) or cumulatively over all collection intervals
$\%\ Dose_{excreted}$	The percentage of given dose excreted in the urine as unchanged drug

1. INTRODUCTION

This statistical analysis plan (SAP) describes the statistical analysis methods and data presentations to be used in tables, figures, and listings in the clinical study report (CSR) for Study GS-US-379-1932. This SAP is based on the study protocol amendment 1 dated 9 January 2017, and the electronic case report form (eCRF). The SAP will be finalized before database finalization. Any changes made after the finalization of the SAP will be documented in the CSR.

1.1. Study Objectives

The primary objective of this study is as follows:

- To evaluate the pharmacokinetics (PK) of GS-9876 in subjects with impaired renal function relative to matched, healthy controls

The secondary objective of this study is as follows:

- To evaluate the safety and tolerability of GS-9876 in subjects with normal and impaired renal function

1.2. Study Endpoints

The primary endpoints are PK parameters AUC_{last}, AUC_{inf}, and C_{max} for GS-9876.

The secondary endpoints include the incidence of adverse events (AEs), laboratory abnormalities, vital sign changes and safety ECG abnormalities.

1.3. Study Design

Study GS-US-379-1932 is an open-label, parallel-group, adaptive, single-dose, multi-center Phase 1 study to evaluate the PK of GS-9876 in subjects with impaired renal function.

This study will target enrolling 20 to 60 subjects using an adaptive design that includes up to 3 enrolled cohorts of subjects with renal impairment and matched healthy controls. Based on safety and PK results from subjects with moderate renal impairment (Cohort 1), subjects with severe renal impairment (Cohort 2) and/or mild renal impairment (Cohort 3) will be enrolled as follows:

- Cohort 1 (Moderate Renal Impairment): Up to 20 subjects (10 per group, moderate renal impairment and matched healthy controls) for 8 evaluable subjects per group.

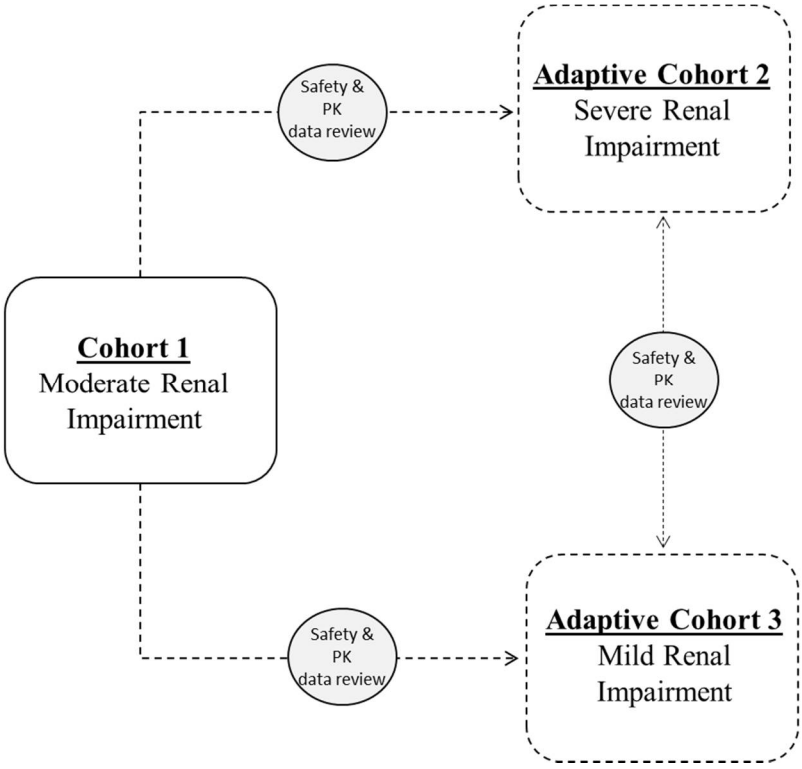
- Adaptive Cohort 2 (Severe Renal Impairment): Up to 20 subjects (10 subjects with severe renal impairment and up to 10 matched healthy control subjects if none of the healthy subjects from a previous cohort is an appropriate match for a severe impairment subject) for 8 evaluable subjects per group.

- Adaptive Cohort 3 (Mild Renal Impairment): Up to 20 subjects (10 subjects with mild renal impairment and up to 10 matched healthy control subjects if none of the healthy subjects from a previous cohort is an appropriate match for a mild impairment subject) for 8 evaluable subjects per group.

Adaptive Cohorts 2 and/or 3 will be enrolled as determined by safety and/or PK data in Cohort 1. Specifically, Cohort 2 (Severe Renal Impairment) will be evaluated if supported by safety and/or PK data from Cohort 1 (Moderate Renal Impairment). Cohort 3 (Mild Renal Impairment) will be evaluated if supported by safety and if substantial changes (≥ 2-fold mean difference from matched controls) in the exposure of GS-9876 is observed in subjects with moderate renal impairment in Cohort 1. Cohorts 2 and 3 may not be enrolled or may be enrolled sequentially or in parallel, as governed by safety and PK data in Cohort 1. Each control subject may be matched to multiple renal impaired subjects across different cohorts and can be matched to only 1 renal impaired subject within a cohort.

An overview of the study design is shown in Figure 1-1.

Figure 1-1. Study Design



The categorization of renal impairment is based on creatinine clearance (CLcr) using the Cockcroft-Gault formula from the screening visit. Specifically, a subject will be considered as having

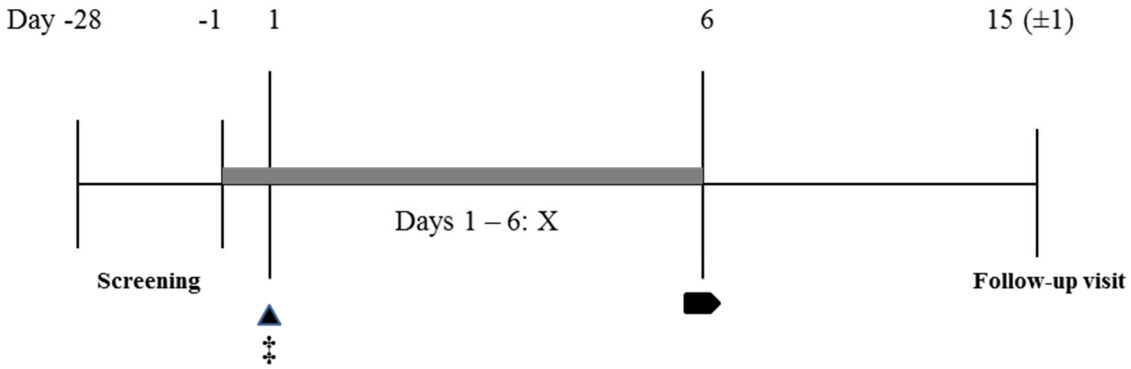
- Mild impairment if CLcr (rounding to the nearest integer) is 60-89 mL/min
- Moderate impairment if CLcr (rounding to the nearest integer) is 30-59 mL/min
- Severe impairment if CLcr (rounding to the nearest integer) is 15-29 mL/min

A subject with CLcr (rounding to the nearest integer) higher than or equal to 90 mL/min is categorized as having normal renal function.

Following screening and Day -1 procedures, eligible subjects will be confined to the study center beginning Day -1 until the completion of assessments on Day 6. Subjects will return 14 (±1) days after last dose for an in-clinic follow up visit (ie, Day 15).

The study schema is shown in Figure 1-2.

Figure 1-2. Study Schema



▲ GS-9876 20 mg
Clinic Confinement
X Intensive PK Samples
Discharge
‡ Matched healthy control subjects will begin dosing after completion of PK assessments (Day 6) for the subject with renal impairment.

Pharmacokinetic Assessments

Plasma PK Assessment

Plasma concentrations of GS-9876 will be measured and PK parameters determined. Plasma concentrations of GS-9876 metabolites may be determined and pharmacokinetics explored, as applicable.

Intensive PK sampling will occur relative to dosing of GS-9876 at the following time points:

- Day 1: 0 (predose), 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 16, 24, 36, 48, 60, 72, 96 and 120 hours postdose

Urine PK Assessment

Urine PK samples will be collected relative to dosing of GS-9876 at the following intervals:

- Day 1: Pre-dose void, 0-6, 6-12, 12-24, 24-48, 48-72, 72-96 and 96-120 hours postdose

Urine concentrations of GS-9876 and/or metabolites may be determined and PK parameters estimated.

Protein Binding Assessment

Protein binding of GS-9876 (and its metabolites, as applicable) will be assessed at or near their T_{max} timepoint(s) as well as another later time point.

Safety Assessments

Safety will be evaluated by assessment of clinical laboratory tests, electrocardiogram (ECG), periodic physical examinations including vital signs at various time points during the study, and by documentation of adverse events (AEs).

Complete physical exam: Screening, Days -1, 6, and at the follow-up visit 14 (±1) days after last dose or at the Early Termination (ET) visit, if applicable

Symptom driven physical exam: every day during confinement as needed, based on reported signs and symptoms

Height: Screening

Weight: Screening and Day -1

Urine Drug and Alcohol Assessments: Screening, Day -1

Serology Test (hepatitis B virus [HBV], hepatitis C virus [HCV], human immunodeficiency virus [HIV]): Screening

Serum Pregnancy Test (women of childbearing potential only): Screening, Day -1, 6, and at the follow-up visit 14 (±1) days after last dose or at the ET visit, if applicable

Vital signs (blood pressure, pulse, respiration rate, and temperature): Screening, Days -1, 1 (predose, 1, 3, 6, and 12 hours postdose), 2, 3, 4, 5, 6, and at the follow-up visit 14 (±1) days after last dose or at the ET visit, if applicable

Clinical laboratory tests (blood chemistry, and urinalysis): Screening, Days -1, 1 (4 hours postdose), 2, 3, 6, and at the follow-up visit 14 (±1) days after last dose or at the ET visit, if applicable

Clinical laboratory tests (hematology and coagulation): Screening, Days -1, 1 (4 hours postdose), 3, 6, and at the follow-up visit 14 (±1) days after last dose or at the ET visit, if applicable.

12-lead ECG: Screening, Days -1, 1 (postdose), 6, and at the follow-up visit 14 (±1) days after last dose or at the ET visit, if applicable

Assessment of AEs and concomitant medications will continue throughout the study.

1.4. Sample Size and Power

With 16 (8 per group) evaluable subjects, the estimated two-sided 90% CI of the GLSM ratio of test versus reference groups, with regards to PK parameters (AUC and C_{max}) would be within (50%, 200%) with over 95% probability. This calculation is based on a two group t-test of equivalence in means at the significance level of 0.05, assuming the expected geometric means ratio of 1.0 and inter-subject standard deviation (SD) of no more than 0.35 on a natural logarithm scale. The assumption about the inter-subject SD is supported by previous Gilead study GS-US-379-1372 using the maximum variability for AUC and C_{max} from the closest dose levels (15 mg and 30 mg) of the dose in this study. An overage of 2 subjects per group will be enrolled to accommodate subject drop-outs, thus requiring a total enrollment of 20 subjects (10 per group) for each cohort.

2. TYPE OF PLANNED ANALYSIS

2.1. Data Monitoring Committee

This study does not have a data monitoring committee.

2.2. Interim Analysis

No formal interim analyses are planned for this study.

2.3. Final Analysis

After all subjects have completed the study, outstanding data queries have been resolved or adjudicated as unresolvable,, and the database has 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, 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. 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.

3.1.1. All Enrolled Analysis Set

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

This is the primary analysis set for listings.

3.1.2. Safety Analysis Set

The Safety Analysis Set includes all enrolled subjects who received GS-9876. This is the primary analysis set for safety tables.

3.1.3. Pharmacokinetic Analysis Set

The PK Analysis Sets include all enrolled subjects who took 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 enrolled subjects. No covariates will be included in analyses.

3.3. Examination of Subject Subsets

There are no prespecified subject subsets for analyses.

3.4. Multiple Comparisons

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

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.

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

- A value that is 1 unit above the LOQ will be used to calculate descriptive statistics if the datum is reported in the form of "> x" (where x is considered the LOQ). Values with decimal points will follow the same logic as 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 lower limit of quantitation (LLOQ) at postdose time points for determination of summary and order statistics.

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."

Pharmacokinetic 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 value off-treatment collected prior to study drug administration.

Postdose value is defined as any value collected after the study drug administration and before the dosing date plus 30 days.

Study Day will be calculated from the date of GS-9876 administration and derived as follows:

- For postdose study days: assessment date –dosing date + 1
- For days prior to the dose: assessment date – dosing date

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

3.7.2. Analysis 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.
- For subjects who prematurely discontinue from the study, ET data will be summarized as a separate visit, labeled 'Early Termination'.

The predose and postdose visits for vital signs for different cohorts are summarized in Table 3-1.

Table 3-1. Predose and Postdose Visits of Vital Signs

Visit Label	Study Day and Time points
Predose	1 (predose)
Day 1	1 (1, 3, 6, and 12 hours postdose)
Day 2	2
Day 3	3
Day 4	4
Day 5	5
Day 6	6
Follow-up	15 (±1)
Early Termination	Early Termination (if applicable)

The predose and postdose visits for laboratory tests for different cohorts are summarized in Table 3-2.

Table 3-2. Predose and Postdose Visits of Laboratory Tests

Visit Label	Study Day and Time points
Predose	-1
Day 1	1 (4 hours postdose)
Day 2	2 (chemistry and urinalysis only)
Day 3	3
Day 6	6
Follow-up	15 (±1)
Early Termination	Early Termination (if applicable)

The predose and postdose visits for ECG for different cohorts are summarized in Table 3-3.

Table 3-3. Predose and Postdose Visits for Electrocardiogram

Visit Label	Study Day and Time points
Predose	-1
Day 1	1
Day 6	6
Follow-up	15 (±1)
Early Termination	Early Termination (if applicable)

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

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

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

- For predose, the last available record on or prior to the date and time of the first dose of study drug will be selected. If there are multiple records with the same time or no time recorded on the same day, average (arithmetic or geometric mean, as appropriate) will be used for the predose value.
- For postdose visits:
  - The record closest to the nominal day for that visit will be selected.
  - If there are 2 records that are equidistant from the nominal day, the later record will be selected.
  - If there is more than 1 record on the selected day, the average will be taken, unless otherwise specified.

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

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

- For postdose visits, if there are multiple records with the same time or no time recorded on the same day, the most conservative value 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 and disposition will be provided by renal function group and by renal function group within each cohort. The number and percentage of subjects in each of the categories listed below will be provided. The denominator for the percentage calculation will be the total number of subjects in the renal function groups included in the All Enrolled Analysis Set.

- Safety Analysis Set
- PK Analysis Set
- Completed study drug
- Did not complete study drug with reasons for study drug discontinuation, as applicable
- Completed study
- Did not complete study with reasons for study discontinuation, as applicable

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

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

- Reasons for premature study drug or study discontinuation

A by-subject listing of subject disposition including renal function group, date of study drug administration (study days), study drug completion status, reason for study drug discontinuation (if applicable), study completion status, reason for study discontinuation (if applicable) will be provided by subject ID number in ascending order.

For a control subject may be matched to multiple renal impaired subjects across different cohorts, a by-subject listing of subject match and cohort affiliation will be provided.

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. Study drug administration data for subjects who received study drug will be listed.

A listing for subjects who were enrolled but not dosed will also be provided.

4.3. Protocol Deviations for Eligibility

A by-subject listing will be provided for the enrolled subject who failed to meet all inclusion criteria or met at least 1 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.

4.4. Important Protocol Deviations

A by-subject listing will be provided for those subjects who had important protocol deviations.

5. BASELINE CHARACTERISTICS

5.1. Demographics

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

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

5.2. Baseline Characteristics

Baseline characteristics include body weight (in kg), height (in cm), and body mass index (BMI; in kg/m^2), CLcr (mL/min) using Cockcroft-Gault formula, and estimated glomerular filtration rate (eGFR) using the Modification of Diet in Renal Disease (MDRD) Study equation {National Institute of Diabetes and Digestive and Kidney Diseases (NIH) 2016}. The equation used for MDRD-based eGFR is as follows:

$$\text{eGFR (mL/min/1.73m}^2\text{)} = 175 \times (S_{cr})^{-1.154} \times (\text{Age})^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if African American}),$$
where S_{cr} is serum creatinine in mg/dL.

These baseline characteristics will be summarized by renal function group (determined based on CLcr value from Cockcroft-Gault formula) using descriptive statistics (numbers of subjects, mean, SD, median, Q1, Q3, minimum, and maximum) for continuous variables and using the numbers and percentages of subjects for categorical variables. For baseline body weight, height, BMI, CLcr and eGFR, descriptive statistics also will be presented by sex in the same table. 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, high-level term, preferred term (PT), and lower-level term will be provided in the AE dataset.

7.1.2. Adverse Event Severity

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

7.1.3. Relationship of Adverse Events to Study Drug

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 relationships 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 "Related" 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 procedures will be considered related to study procedures for summary purposes. However, by-subject data listings will show the relationship as missing from that captured on the CRF.

7.1.5. Serious Adverse Events

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

7.1.6. Treatment-Emergent Adverse Events

7.1.6.1. Definition of Treatment Emergent

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

- Any AEs with an onset date on or after the study drug start date and no later than 30 days after permanent discontinuation of study drug. 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, and renal function group based on the Safety Analysis Set as follows:

- All TEAEs

- All TEAEs by SOC and PT

- All TEAEs by severity

- All treatment-related AEs

- All TEAEs of Grade 2 or higher
- All treatment-related AEs by severity
- All treatment-emergent SAEs
- All treatment-related SAEs
- All TEAEs leading to study discontinuation

A brief, high-level summary of AEs described above will be provided by renal 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 most severe grade will be used for those AEs that occurred more than once in an individual subject per treatment during the study.

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

- All AEs (indicating whether the event is treatment emergent)
- All SAEs
- Deaths

7.1.8. Additional Analysis of Adverse Events

No additional analysis of AEs 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 time point in chronological order for hematology, chemistry, and urinalysis separately. Values falling outside of the relevant reference range and/or having a severity grade of 1 or higher on the protocol specified severity grading will be flagged in the data listings, as appropriate.

No inferential statistical testing is planned for laboratory assessments.

7.2.1. Summaries of Numeric Laboratory Results

Descriptive statistics will be provided by renal function group for each laboratory test as follows:

- Predose values
- Values at each postdose time point
- Change from predose at each postdose time point

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 Common Toxicity Criteria for Adverse Events (CTCAE) Version 4.03 will be used to assign toxicity grades 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 assessment at any postdose 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 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 time point.

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

- Treatment-emergent Graded laboratory abnormalities

- Treatment-emergent Grade 3 or higher 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 time point 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. Body Weight, Height, BMI and Vital Signs

Descriptive statistics will be provided by renal function group for vital signs (including body temperature, pulse rate, respiratory rate, systolic and diastolic blood pressure) as specified below:

- Predose value
- Values at each postdose time point
- Change from predose at each postdose time point

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 inferential statistical testing is planned.

A by-subject listing of vital signs will be provided by subject ID number and time point in chronological order. Body weight, height, and BMI will be included in the vital signs listing, if space permits, otherwise they will be provided separately.

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. Electrocardiogram Results

7.5.1. Investigator Electrocardiogram Assessment

A shift table of the investigator's assessment of ECG results at each scheduled visit compared with predose values will be presented by renal 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 time point in chronological order.

7.6. Other Safety Measures

A by-subject listing of subject pregnancies during the study will be provided by subject ID number. No additional safety measures are specified in the protocol.

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

7.7. Changes From Protocol-Specified Safety Analyses

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

8. PHARMACOKINETIC EVALUATION/ANALYSIS

8.1. Estimation of Pharmacokinetic Parameters

Pharmacokinetic parameters will be estimated using Phoenix WinNonlin® software using standard noncompartmental methods. The linear/log trapezoidal 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 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.

Renal clearance (CLr) will be derived by dividing amount excreted in urine (Ae) through t hours postdose (eg. t = 120 hrs) by AUC_0-t (eg. AUC_{0-120}). The determination of t will be based on the availability of data and assessed by the PK scientist. Fraction excreted unchanged through t hours postdose (fe_{0-t}) will be derived by dividing amount excreted in urine (Ae, µg) through the last urine sampling timepoint over the dose (mg) administered. A conversion factor may be deployed to adjust the differences in reported units before deriving CLr and fe_{0-t}. For example, if the units of Ae, AUC_{0-t}, and the dose are µg, h*ng/mL, and mg, respectively, the following equations will be utilized:

$$CLr\ (mL/min) = (Ae \times 1000) / (60 \times AUC0\text{-}t);$$

$$fe0\text{-}t = 100 \times Ae / (Dose \times 1000).$$

8.1.1. Pharmacokinetic Parameters

Pharmacokinetic parameters for GS-9876 will be generated for all subjects for whom parameters can be derived.

The parameters presented in Table 8-1 and Table 8-2 will be used to evaluate the PK objectives of the study. The primary parameters are plasma PK parameters AUC_{last}, AUC_{inf}, and C_{max} of

GS-9876. The PK parameters to be estimated in this study are listed and defined in PK Abbreviations section.

Table 8-1. Plasma Pharmacokinetic Parameters

Analyte	Parameters
GS-9876	AUC_{last}, AUC_{inf}, $\%AUC_{exp}$, C_{max}, T_{max}, C_{last}, T_{last}, λ_z, CL/F, V_z/F, and $t_{1/2}$, as applicable

Table 8-2. Urine Pharmacokinetic Parameters

Analyte	Parameters
GS-9876	CL_r, A_e, and fe, as applicable

8.2. Statistical Analysis Methods

8.2.1. General considerations

Individual subject concentration data and individual subject PK parameters including percentage of protein binding for GS-9876 will be listed and summarized using descriptive statistics by renal function group. Summary statistics (numbers of subjects, mean, SD, coefficient of variation, median, minimum, maximum, Q1, and Q3) will be presented for both individual subject concentration data by time point and individual subject PK parameters by renal function group. 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 zero at predose and one-half of the 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.

In addition to the renal function categorization based on CLcr throughout this study, MDRD-based eGFR will be used for subject categorization in PK analysis. Subjects from all cohorts will be pooled and regrouped according to their MDRD-based eGFR values as follows:

- Normal renal function if eGFR (rounding to the nearest integer) is ≥ 90 mL/min/1.73m^2
- Mild impairment if eGFR (rounding to the nearest integer) is 60-89 mL/min/1.73m^2
- Moderate impairment if eGFR (rounding to the nearest integer) is 30-59 mL/min/1.73m^2

- Severe impairment if eGFR (rounding to the nearest integer) is 15-29 mL/min/1.73m^2
- End stage renal impairment if eGFR (rounding to the nearest integer) is ≤ 14 mL/min/1.73m^2

The following tables will be provided for GS-9876 by two sets of categorization (CLcr and MDRD-based eGFR) of renal function group:

- Individual subject concentration data and summary statistics
- Individual subject plasma PK parameters and summary statistics

The following figures will be provided for GS-9876 by two sets of categorization of renal function group:

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

A figure of individual subject concentration data versus time (on linear and semilogarithmic scales) will be provided.

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

The following listings will be provided:

- Pharmacokinetic sampling details by subject, including differences in scheduled and actual draw times, and sample age
- Individual data on determination of plasma half-life and corresponding regression correlation coefficient

8.2.2. Statistical Methodology

The statistical comparisons of the natural log-transformed PK parameters for GS-9876 between renal impaired subjects and healthy controls will be performed. All subjects with available data for the PK parameter under evaluation will be included in the modeling.

Consistent with using two sets of renal function categorization in PK summaries, two corresponding sets of comparisons will be performed. Details of these comparisons are shown in Table 8-3. To ensure the appropriateness of applications of statistical testing, the comparisons will only be implemented when there are at least 3 subjects in both test and reference groups. The ratio of geometric least squares means (GLSMs) for the PK parameter in comparison between the test and reference groups and the 90% CI for the ratio will be provided.

Table 8-3. Statistical Comparisons for Pharmacokinetic Analysis of Normal and Impaired Renal Function

Renal Function Categorization	Parameter	Comparison	
		Test Group	Reference Group
Creatinine Clearance (rounding to the nearest integer)	AUC_{inf}, AUC_{last}, C_{max}	Mild Impairment CLcr 60-89 mL/min	Normal CLcr ≥ 90 mL/min
	AUC_{inf}, AUC_{last}, C_{max}	Moderate Impairment CLcr 30-59 mL/min	Normal CLcr ≥ 90 mL/min
	AUC_{inf}, AUC_{last}, C_{max}	Severe Impairment CLcr 15-29 mL/min	Normal CLcr ≥ 90 mL/min
MDRD-based eGFR (rounding to the nearest integer)	AUC_{inf}, AUC_{last}, C_{max}	Mild Impairment eGFR 60-89 mL/min/1.73m^2	Normal eGFR ≥ 90 mL/min/1.73m^2
	AUC_{inf}, AUC_{last}, C_{max}	Moderate Impairment eGFR 30-59 mL/min/1.73m^2	Normal eGFR ≥ 90 mL/min/1.73m^2
	AUC_{inf}, AUC_{last}, C_{max}	Severe Impairment eGFR 15-29 mL/min/1.73m^2	Normal eGFR ≥ 90 mL/min/1.73m^2
	AUC_{inf}, AUC_{last}, C_{max}	End Stage Impairment eGFR ≤ 14 mL/min/1.73m^2	Normal eGFR ≥ 90 mL/min/1.73m^2

For each PK parameter in comparison, a parametric (normal theory) analysis of variance (ANOVA) model will be fitted to the natural log-transformed values of PK parameter under evaluation. The statistical model will include renal function group as a fixed effect.

The following SAS PROC MIXED code will provide the group comparison analysis between the renal function groups and the 90% CI calculations for natural log-transformed PK parameters.

```
proc mixed;
  class renalgrp subjid;
  model lnest = renalgrp / ddfm=kr;
  repeated / group = renalgrp;
  lsmeans renalgrp / e diff cl alpha = 0.1;
  estimate 'Impaired versus Normal' treat 1 -1 / cl alpha = 0.10;
  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 (GLSM ratio) and associated 90% CI will be calculated by taking the exponential of the point estimate and the corresponding lower and upper limits, which is consistent with the two 1-sided tests approach {U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) 2001, U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) 2003}.

Nonparametric analyses for the PK parameters CL/F, Vz/F, and $t_{1/2}$, are routinely performed. When needed, these analyses can be performed using the Wilcoxon rank sum test for parallel design between the test and reference groups for GS-9876.

The following SAS PROC NPARLWAY code will provide the comparison.

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

To evaluate the protein binding of GS-9876, the percent of unbound GS-9876 at T_{max} and a later time point will be summarized by time point and renal function group. Protein binding data for individual subject will be presented in a listing.

8.3. 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

National Institute of Diabetes and Digestive and Kidney Diseases (NIH). Estimating Glomerular Filtration Rate (GFR). Available at: https://www.niddk.nih.gov/health-information/health-communication-programs/nkdep/lab-evaluation/gfr/estimating/Pages/estimating.aspx. Accessed 06 October. 2016:

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, Mountain View, CA, USA.

11. SAP REVISION

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

12. APPENDICES

Appendix 1. Schedule of Assessments

Study Procedure	Screen[a]	Day −1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6[b]	Day 15 (±1) Follow-Up[c]	ET[d]
Written Informed Consent	X									
Medical History	X									
Complete Physical Exam	X	X						X	X	X
Symptom-Driven Physical Examination[e]			X	X	X	X	X			
Height	X									
Weight	X	X								
Vital Signs[f]	X	X	X	X	X	X	X	X	X	X
HIV-1, HBV, and HCV Testing	X									
Hematology[g]	X	X	X		X			X	X	X
Coagulation	X	X	X		X			X	X	X
Chemistry[h]	X	X	X	X	X			X	X	X
Urinalysis	X	X	X	X	X			X	X	X
Serum Pregnancy Test[i]	X	X						X	X	X
Creatinine Clearance	X	X								
Urine Drug and Alcohol Screen	X	X								
12-Lead ECG	X	X	X					X	X	X
Study Drug Administration			X							
Intensive Plasma PK[j]			X	X	X	X	X	X		

Study Procedure	Screen[a]	Day −1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6[b]	Day 15 (±1) Follow-Up[c]	ET[d]
Urine PK[k]			X	X	X	X	X	X		
Review Study Restrictions	X	X						X	X	
Clinic Confinement		X	X	X	X	X	X			
Review AEs & Concomitant Medications[l]	X	X	X	X	X	X	X	X	X	X

a Prospective subjects should be screened no more than 28 days prior to administration of the first dose of study drug.
b Subjects will be discharged from the clinic on Day 6, following all morning assessments.
c 14(± 1) days after the last administration of study drug, all subjects will return for an in-clinic follow-up visit and complete procedures as outlines.
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 Vital signs include blood pressure, heart rate, respiration rate, and temperature.
g Hematology: CBC with differential.
h See Protocol Amendment 1 Section 6.9.5 for specifics.
i Females of child-bearing potential only.
j Intensive PK sampling will occur relative to the morning dosing of GS-9876 at the following time points:
Day 1: 0 (predose), 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 16, 24, 36, 48, 60, 72, 96 and 120 hours postdose.
k All urine voided will be collected and pooled relative to dosing of GS-9876 at the following collection intervals:
Day 1: Predose void, 0-6, 6-12, 12-24, 24-48, 48-72, 72-96, and 96-120 hours postdose
l 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 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 eCRF.

GS-US-379-1932 Final SAP

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Biostatistics eSigned	14-Feb-2019 19:28:48
PPD	Clinical Research eSigned	16-Feb-2019 04:38:36
PPD	Clinical Pharmacology eSigned	19-Feb-2019 19:21:57