# STATISTICAL ANALYSIS PLAN

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|---|---|
| **Study Title:** | A Phase 1 Study to Evaluate OATP Transporter-Mediated Drug-Drug Interactions Between Filgotinib and Statins as Probe Drugs in Healthy Participants |
| **Study Phase** | 1 |
| **Name of Test Drug:** | Filgotinib |
| **Study Number:** | GS-US-417-5937 |
| **Sponsor:** | Gilead Sciences, Inc. |
| **Protocol Version (Date):** | Original (25 September 2020) |
| **Analysis Type:** | Final Analysis |
| **Analysis Plan Version:** | Version 1.0 |
| **Analysis Plan Date:** | 23 February 2021 |
| **Analysis Plan Author(s):** | PPD |

**CONFIDENTIAL AND PROPRIETARY INFORMATION**

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# LIST OF ABBREVIATIONS

| | |
|---|---|
| AE | adverse event |
| ATV | atorvastatin |
| BLQ | below the limit of quantitation |
| BCRP | breast cancer resistance proteins |
| BMI | body mass index |
| CI | confidence interval |
| COVID-19 RT-PCR | a real-time reverse transcription polymerase chain reaction (rTT-PCR) test for the qualitative detection of nucleic acid from SARS-CoV-2 |
| CRF | case report form |
| CSR | clinical study report |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CV | coefficient of variation |
| CYP3A | cytochrome P450 3A |
| DDI | drug-drug interaction |
| DMC | data monitoring committee |
| ECG | electrocardiogram |
| eCRF | electronic case report form |
| ET | early termination |
| FIL | filgotinib |
| Gilead | Gilead Sciences |
| GLSM | geometric least-squares mean |
| LLOQ | lower limit of quantitation |
| LOQ | limit of quantitation |
| MedDRA | Medical Dictionary for Regulatory Activities |
| OATP | organic anion transporting polypeptide |
| PT | preferred term |
| PRO | pravastatin |
| Q1, Q3 | first quartile, third quartile |
| RA | rheumatoid arthritis |
| ROS | rosuvastatin |
| SAP | statistical analysis plan |
| SD | standard deviation |
| SI | International System of Units (Systeme International d'Unites) |
| SOC | system organ class |
| TEAE | treatment-emergent adverse events |
| TFLs | tables, figures, and listings |
| TOST | two one-sided tests |
| ULOQ | upper limit of quantitation |
| WHO | World Health Organization |

# PHARMACOKINETIC ABBREVIATIONS

| | |
|---|---|
| $\lambda_Z$ | terminal elimination rate constant, estimated by linear regression of the terminal elimination phase of the log plasma/serum concentration of drug versus time curve of the drug |
| $\%AUC_{exp}$ | percentage of AUC extrapolated between $AUC_{last}$ and $AUC_{inf}$ |
| AUC | area under the plasma/serum concentration versus time curve |
| $AUC_{last}$ | area under the plasma/serum concentration versus time curve from time zero to the last quantifiable concentration |
| $AUC_{inf}$ | area under the plasma/serum concentration versus time curve extrapolated to infinite time, calculated as $AUC_{last} + (C_{last} / \lambda_z)$ |
| $AUC_{xxx}$ | partial area under the plasma/serum concentration versus time curve from time "x" to time "xx" |
| CL/F | apparent oral clearance after administration of the drug: CL/F = Dose/ $AUC_{inf}$, where "Dose" is the dose of the drug |
| $C_{last}$ | last observed quantifiable plasma/serum concentration of the drug |
| $C_{max}$ | maximum observed plasma/serum concentration of drug |
| $C_{min}$ | minimum observed plasma/serum concentration of drug |
| PK | pharmacokinetic(s) |
| $t_{½}$ | 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 ($\lambda_z$) |
| $T_{last}$ | time (observed time point) of $C_{last}$ |
| $T_{max}$ | time (observed time point) of $C_{max}$ |

# 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-417-5937. This SAP is based on the original study protocol dated 25 September 2020 and the electronic case report form (eCRF). The SAP will be finalized prior to database finalization. Any changes made after finalization of the SAP will be documented in the CSR.

## 1.1. Study Objectives

The primary objective of this study is as follows:

- To evaluate the effect of filgotinib (FIL) on a mixed organic anion transporting polypeptide/cytochrome P450 3A (OATP/CYP3A), organic anion transporting polypeptide/ breast cancer resistance protein (OATP/BCRP), and OATP substrates using phenotypic probes

The secondary objective of this study is as follows:

- To evaluate the safety and tolerability of multiple filgotinib doses administered alone or in combination with probe drugs.

## 1.2. Study Endpoints

The primary endpoints are the pharmacokinetic (PK) parameters: $AUC_{last}$, $AUC_{inf}$, and $C_{max}$ of atorvastatin (ATV), ATV's metabolite (2-OH-ATV), pravastatin (PRA), and rosuvastatin (ROS).

The secondary endpoints are as follows:

- Incidences of adverse events (AEs)
- Laboratory abnormalities
- Vital signs

## 1.3. Study Design

This study is a Phase 1, randomized, two-way crossover, open-label, single and multiple dose, single center study to evaluate the effect of filgotinib on a mixed OATP/CYP3A, OATP/BCRP, and OATP substrates using phenotypic probes in healthy normal subjects. Up to 30 subjects will enrolled.

Healthy surgically sterile male and nonpregnant, nonlactating female subjects aged 18 through 55 years old will be enrolled into the study.

Following completion of screening and admission assessments (Day −1), eligible subjects will be randomized at 1:1 ratio on the evening of Day −1 to receive 1 of 2 treatment sequences starting on Day 1. Subjects will dose for 13 days. The treatment end dates are on Day 17 (Sequence AB) or Day 20 (Sequence BA). The completion of assessments is on Day 17 (Sequence AB) or Day 23 (Sequence BA). All subjects will be contacted by telephone 7 (± 2) days after last dose for follow up. The treatment schema is shown below in Figure 1-1.

The study drugs and treatments are as follows:

**OATP/CYP3A substrate:** Atorvastatin (ATV) 40 mg

**OATP substrate:** Pravastatin (PRA) 40 mg

**OATP/BCRP substrate:** Rosuvastatin (ROS) 10 mg

Pravastatin/Rosuvastatin (PRA/ROS) will be coadministered as a probe cocktail.

**Treatment A:** Single dose of ATV 40 mg, followed by a washout period of 1 day and then a single dose of the PRA 40 mg/ROS 10 mg cocktail. All agents should be administered in the morning under fasted conditions.

**Treatment B:** Filgotinib 200 mg administered once daily for 11 days, with a single dose of ATV 40 mg administered on the sixth day followed by a single dose of PRA 40 mg/ROS 10 mg cocktail administered on the eighth day. All agents should be administered in the morning under fasted conditions.

**Table 1-1. Treatment Schema**

| Sequence | Days | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| AB | Period 1 | | | | Period 2 | | | | |
| | 1 | 2 | 3 | 4-6 | 7-11 | 12 | 13 | 14 | 15-17 |
| | ATV | WO | PRA + ROS | WO | FIL | FIL+ ATV | FIL | FIL + PRA + ROS | FIL |
| BA | Period 1 | | | | | | Period 2 | | |
| | 1-5 | 6 | 7 | 8 | 9-11 | 12-17 | 18 | 19 | 20 |
| | FIL | FIL + ATV | FIL | FIL + PRA + ROS | FIL | WO | ATV | WO | PRA + ROS |

FIL = filgotinib; ATV = atorvastatin; PRA = pravastatin; ROS = rosuvastatin; WO=wash out

An overview of the study design is described below and shown in Figure 1-1 and Figure 1-2.

**Figure 1-1. Study Schema – Sequence AB**

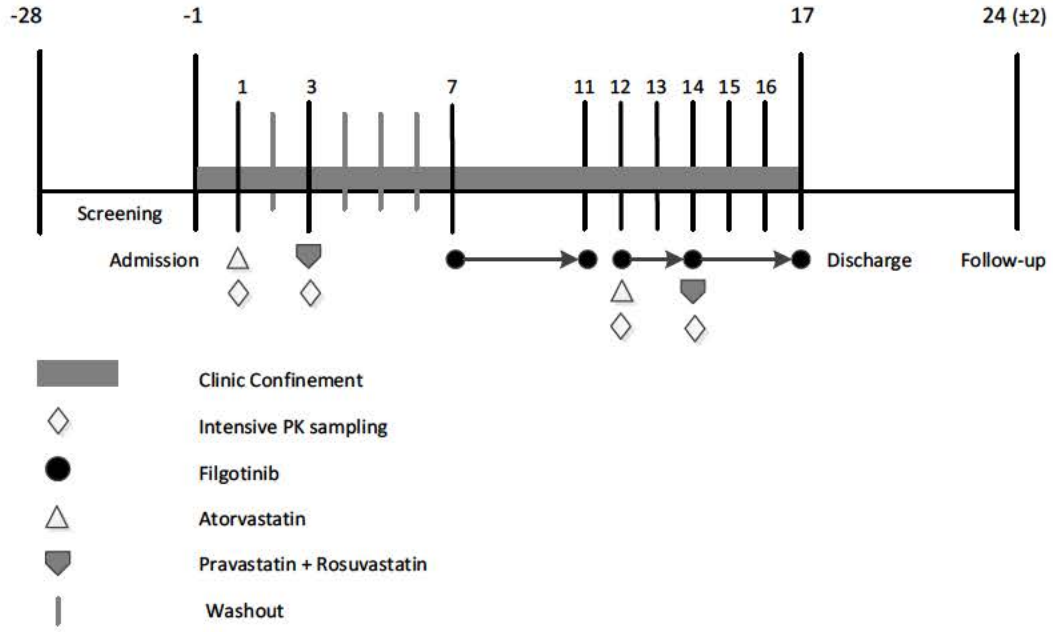
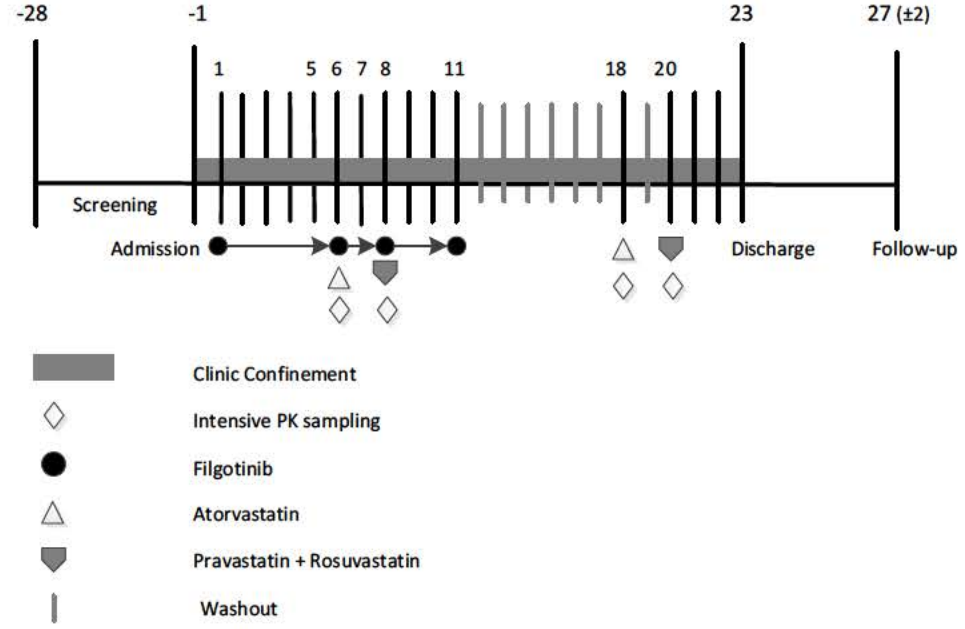



**Figure 1-2. Study Schema – Sequence BA**



**Pharmacokinetic Assessments**

**Plasma Pharmacokinetic Collection**

Plasma concentrations of ATV, 2-OH-ATV, PRA, and ROS will be determined and PK parameters will be evaluated. Plasma concentrations of filgotinib and its metabolite (GS-829845) may be analyzed. Intensive PK sampling will occur relative to dosing of study drug at the following time points. Details regarding study assessment can be found in Appendix 1 and Appendix 2.

**Sequence AB:**

- Days 1 and 12: 0 (predose, ≤ 5 minutes), 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, and 48 hours postdose
- Days 3 and 14: 0 (predose, ≤ 5 minutes), 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 48, and 72 hours postdose

**Sequence BA:**

- Days 6 and 18: 0 (predose, ≤ 5 minutes), 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, and 48 hours postdose
- Days 8 and 20: 0 (predose, ≤ 5 minutes), 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 48, and 72 hours postdose

**Genomic Sample Collection**

A mandatory blood sample will be collected from all subjects who have provided consent to participate in this study. This sample will be collected for the extraction of DNA for genomic testing and genotyping to identify polymorphisms of drug transporters (eg, OATP1B1). This sample should be collected on Day 1, before administration of the first dose of study drug, but may be collected at any time during the study, if necessary.

**Safety Assessments**

Safety will be evaluated throughout the study. Details regarding study assessments can be found in Appendix 1 and Appendix 2.

## 1.4. Sample Size and Power

With 26 evaluable subjects (13 in each sequence), the estimated two-sided 90% CI of the GLSM ratio of test versus reference treatments, with regards to $AUC_{inf}$, $AUC_{last}$, and $C_{max}$, will be within [70%, 143%] with ≥ 85% probability, if the true GLSM ratio is 1.0. This is assuming a standard deviation (SD) of differences of no more than 0.569 on a natural logarithm scale, supported by PK data from Study GS-US-402-2102. With 4 subjects for overage, a total sample size of 30 subjects will be required.

# 2. TYPE OF PLANNED ANALYSIS

## 2.1. Data Monitoring Committee Analyses

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

## 2.2. Interim Analysis

No interim analysis is planned.

## 2.3. Final Analysis

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

## 2.4. Changes from Protocol-Specified Analysis

No changes from protocol-specified analyses are planned.

# 3. GENERAL CONSIDERATIONS FOR DATA ANALYSES

Analysis results will be presented using descriptive statistics. For categorical variables, the number and percentage of subjects in each category will be presented; for continuous variables, the number of subjects (n), mean, standard deviation (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 Randomized Analysis Set and sorted by subject identification (ID) number in ascending order, visit date, and time (if applicable), unless otherwise specified. Data collected on log forms, such as AEs, will be presented in chronological order within subject. The treatment group and treatment sequence to which subjects were initially assigned will be used in the listings.

## 3.1. Analysis Sets

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

For each analysis set, the number and percentage of subjects eligible for inclusion will be provided in the disposition table as detailed in Section 4. A listing of reasons for exclusion from analysis sets will be provided by subject.

### 3.1.1. All Randomized Analysis Set

The All Randomized Analysis Set includes all subjects randomized into the study after screening. This is the primary analysis set for safety listings.

### 3.1.2. Safety Analysis Set

The Safety Analysis Set will include all randomized subjects who received at least 1 dose of study drug. Subjects who received treatment other than that to which they were assigned will be analyzed according to the treatment received. This is the primary analysis set for safety analyses.

### 3.1.3. Pharmacokinetic Analysis Set

The PK Analysis Set will include all randomized subjects who received at least 1 dose of study drug and had at least 1 non-missing PK concentration datum reported by PK laboratory for each respective analyte. This is the primary analysis set for all PK analyses.

## 3.2. Missing Data and Outliers

### 3.2.1. 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.

### 3.2.2. 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.

## 3.3. 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 birthday.

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

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

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

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 plasma concentrations and analysis of PK parameters. Plasma concentration values that are below the limit of quantitation (BLQ) will be presented as "BLQ" in the concentration data listing. Values that are BLQ will be treated as 0 at predose time points, and one-half the value of the 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 given time point, the minimum and Q1 values will be displayed as "BLQ."

If more than 50% of the subjects have a concentration data value of BLQ for a given time point, the minimum, Q1, and median values will be displayed as "BLQ."

- If more than 75% of the subjects have a concentration data value of BLQ for a given time point, the minimum, Q1, median, and Q3 values will be displayed as "BLQ."

- If all subjects have concentration data values of BLQ for a given time point, all order statistics (minimum, Q1, median, Q3, and maximum) and summary statistics will be displayed as "BLQ."

PK parameters that are BLQ will be imputed as one-half the value of lower limit of quantitation (LLOQ) before log transformation or statistical model fitting.

## 3.4. Visit Windows

### 3.4.1. Definition of Predose, Postdose, Study day, and Treatment Day

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

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

Study Day is the day relative to the date of the first dose of study drug administration.

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

- For postdose study days: assessment date – first dosing date + 1

- For days prior to the first dose: assessment date – first dosing date

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

Treatment Day is the day relative to the first dose of study drug administration in each period. Treatment Day 1 will be defined as the first dosing date of study drug in each period. Treatment Day will only be used in PK-related listings.

Treatment Day will be calculated from the date of first dose of study drug administration in each period and derived as follows:

- For postdose treatment days: assessment date – first dosing date in each period + 1

- For days prior to the first dose: assessment date – first dosing date in each period.

### 3.4.2. Analysis Window

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 but will be listed in the listings. 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 Visit.'
- For laboratory abnormalities, all postdose values (including scheduled and unscheduled visits) will be used to assess the maximum toxicity.
- For vitals assessments, all postdose values (including scheduled and unscheduled visits) will be used to assess maximum postdose and maximum postdose change.

### 3.4.3. 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, non-missing numeric observations exist on a day, records will be chosen based on the following rules if a single value is needed:

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

- For postdose values, 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 (e.g., abnormal will be selected over normal for safety findings).

# 4. SUBJECT DISPOSITION

## 4.1. Subject Enrollment and Disposition

A summary of subject enrollment (randomization) and disposition will be provided by treatment sequence 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. For the Safety Analysis Set category, the denominator for the percentage calculation will be the total number of subjects randomized for each column using All Randomized Analysis Set. For all other categories, the denominator for the percentage calculation will be the total number of subjects in the Safety Analysis Set for each column.

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

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

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

- Reasons for premature discontinuation of study drug or study

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

## 4.2. Extent of Exposure

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

## 4.3. Protocol Deviations

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

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

# 5. BASELINE CHARACTERISTICS

## 5.1. Demographics

Subject demographic variables (ie, age, sex, race, and ethnicity) will be summarized by treatment sequence and overall using descriptive statistics for continuous variables and using number and percentage of subjects for categorical variables. 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 creatine clearance (as measured by Cockcroft-Gault equation) {Cockcroft 1976}), height, BMI, body weight, and blood tests. These baseline characteristics will be summarized by treatment sequence and overall using descriptive statistics for continuous variables and using number and percentage of subjects for categorical variables. The summary of baseline characteristics will be provided for the Safety Analysis Set. No formal statistical testing is planned.

A by-subject listing of 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.

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 adverse events (AEs) will be coded using Medical Dictionary for Regulatory Activities (MedDRA) 23.1. 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 using the Common Terminology Criteria for Adverse Events (CTCAE) Toxicity Grading Scale, Version 5. The severity grade of events for which the investigator did not record severity will be categorized as "missing" for tabular summaries and data listings. The missing category will be presented last in the summary presentation.

### 7.1.3. Relationship of Adverse Events to Study Drug

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

### 7.1.4. Relationship of Adverse Events to Study Procedure

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

### 7.1.5. Serious Adverse Events

Serious adverse events (SAEs) will be identified and captured as SAEs if the AEs met the definition of SAEs that were specified in the study protocol. Serious adverse events captured and stored in the clinical database will be reconciled with the SAE database from the Global Patient Safety 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 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, 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.

TEAEs with an onset date on/after previous treatment administration date and prior to the next treatment administration date will be attributed to the previous treatment.

#### 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

The number and percentage of subjects who experienced at least 1 TEAE will be provided and summarized by SOC and PT, and by treatment sequence with treatments listed thereunder based on the Safety Analysis Set as follows:

- All TEAEs
- All TEAEs related to study drug
- All TEAEs related to study procedures
- All TEAEs by severity

- TEAEs of Grade 3 or higher
- All TEAEs related to study drug by severity
- All SAEs
- All SAEs related to study drug
- All TEAEs leading to premature discontinuation of study drug
- Death

There will be two ways to summarize AEs:

1) Two treatment sequences will be combined. And the same treatment (FIL, ATV, etc.) from different treatment sequence will be pooled together.

2) Two treatment sequences will be summarized separately.

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

Multiple events will be counted only once per subject per treatment in each summary. An AE that starts in one treatment period and continues into the following treatment period(s) will be counted only in the period in which the AE began. 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, and the alphabetic order of PT will be applied within the same frequency. For summaries by grade, 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 to the above summary tables, all TEAEs and SAEs will be summarized by PT only, in descending order of total frequency and the alphabetic order within the same frequency.

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

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

### 7.1.8. Additional Analysis of Adverse Events

No additional analysis of adverse events is planned.

## 7.2. Laboratory Evaluations

Laboratory data collected during the study will be analyzed and summarized using both quantitative and qualitative methods. Summaries of laboratory data will be provided for the Safety Analysis Set and will include data collected up to the last dose of study drug plus 30 days for subjects who have permanently discontinued study drug. The analysis will be based on values reported in conventional units. When values are BLQ, the imputed value will be used for the purpose of calculating summary statistics. If a lab value is reported using a non-numeric qualifier (eg, less than (<) a certain value, or greater than (>) a certain value), the given numeric value will be used in the summarization and will be listed. Both of them will be listed as such.

The Incidence of treatment-emergent graded laboratory abnormalities will be summarized by treatment sequence with treatments listed thereunder.

A by-subject listing for laboratory test results will be provided by subject ID number and time point in chronological order for hematology, serum chemistry (fasting) and urinalysis separately. Values falling outside of the relevant reference range and/or having a severity grade of 1 or higher on the Gilead Grading Scale for Severity of Adverse Events and Laboratory Abnormalities and treatment emergent graded laboratory abnormalities will be flagged in the data listings, as appropriate.

Listings by subjects for Serum pregnancy test (females of childbearing potential only), Hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus type 1 testing (HIV-1), Follicle Stimulating Hormone (FSH), Thyroid stimulating hormone testing (screening only), and Urine drug and alcohol assessments at screening will also be provided.

Separate by-subject listing of treatment-emergent laboratory abnormalities and treatment-emergent grade 3 or higher laboratory abnormalities will be provided by subject ID number and visit in chronological order. These listing will include all test results that were collected throughout the study for the laboratory test(s) of interest, with all applicable severity grades displayed.

No inferential statistics will be generated.

### 7.2.1. Summaries of Numeric Laboratory Results

Descriptive statistics will be provided by treatment sequence for all laboratory test specified in the study protocol as follows:

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

Predose and postdose values will be defined as described in Section 3.4. 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 3.4.2.

### 7.2.2. Graded Laboratory Values

The CTCAE Version 5.0 will be used to assign toxicity grades (0 to 4) to laboratory results for analysis. Grade 0 includes all values that do not meet the criteria for an abnormality of at least Grade 1. For laboratory tests with criteria for both increased and decreased levels, analyses for each direction (ie, increased, decreased) will be presented separately.

#### 7.2.2.1. Treatment-Emergent Laboratory Abnormalities

Treatment-emergent laboratory abnormalities are defined as values that increase at least 1 toxicity grade from predose at any postdose 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 Treatment-emergent Laboratory Abnormalities

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

- Treatment-emergent graded laboratory abnormalities
- Treatment-emergent grade 3 or higher laboratory abnormalities

There will be two ways to summarize treatment-emergent laboratory abnormalities:

3) Two treatment sequences will be combined. And the same treatment (FIL, ATV, etc.) from different treatment sequence will be pooled together.

4) Two treatment sequences will be summarized separately.

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.

### 7.2.3. Liver-Related Laboratory Evaluations

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

- Aspartate aminotransferase (AST): (a) > 3 times of the upper limit of reference range (ULN); (b) > 5 × ULN; (c) > 10 × ULN; (d) > 20 × ULN
- Alanine aminotransferase (ALT): (a) > 3 × ULN; (b) > 5 × ULN; (c) > 10 × ULN; (d) > 20 × ULN
- AST or ALT: (a) > 3 × ULN; (b) > 5 × ULN; (c) > 10 × ULN; (d) > 20 × ULN
- Total bilirubin: > 2 × ULN
- Alkaline phosphatase (ALP) > 1.5 × ULN
- AST or ALT > 3 × ULN and total bilirubin: (a) > 1.5 × ULN; (b) > 2 × ULN

The summary will be provided by treatment sequence with treatments listed thereunder.

There will be two ways to summarize liver-related laboratory abnormalities:

5) Two treatment sequences will be combined. And the same treatment (FIL, ATV, etc.) from different treatment sequence will be pooled together.
6) Two treatment sequences will be summarized separately.

The summary will include data from all postdose 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 postdose values. For both the composite endpoint of AST or ALT and total bilirubin, subjects will be counted once when the criteria are met at the same postdose visit date. The denominator is the number of subjects in the Safety Analysis Set who have nonmissing postdose values of all relevant tests at the same postdose visit date. A listing of subjects who met at least 1 of the above criteria will be provided.

## 7.3. Body Weight, Height, BMI, and Vital Signs

Descriptive statistics will be provided by treatment sequence for body weight, BMI, and vital signs as follows:

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

In addition, descriptive statistics will be provided by treatment sequence for height at baseline only.

Predose and postdose values will be defined as described in Section 3.4. 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 3.4.2. No inferential statistics will be generated.

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. Prior and Concomitant Medications

Medications collected at screening, admission (Day -1) and during the study will be coded using the BMAR20 version of the World Health Organization (WHO) Drug dictionary.

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

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

### 7.5. Electrocardiogram Results

Electrocardiogram (ECG) data will not be presented in the CSR since ECGs were not assessed in this study other than as part of the screening process for potential new subjects.

A by-subject listing for ECG assessment results will be provided.

### 7.6. Other Safety Measures

By-subject listings for creatine clearance test results and physical examination findings during the study will be provided by subject ID number.

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

If any of below events related to COVID-19 occurs, a by-subject listing may be provided by subject identification (ID) number in ascending order to show:

- Reasons for premature study drug or study discontinuation due to COVID-19
- Important protocol deviations related to COVID-19
- AEs related to COVID-19

Premature study drug or study discontinuation due to COVID-19 is identified either with reason of AE, and AE is COVID-19 related, or with reason of other than AE, and description contains key word “COVID”.

IPD related to COVID-19 is identified by searching description with key word “COVID”.

AE’s related to COVID-19.

Vital sign will only be summarized by treatment sequence, not treatment.

Electrocardiogram assessments will not be summarized by treatment or treatment sequence, as they will only be performed as part of the screening process.

# 8. PHARMACOKINETIC EVALUATION/ANALYSIS

## 8.1. Estimation of Pharmacokinetic Parameters

Pharmacokinetic parameters will be estimated using Phoenix WinNonlin® software using standard noncompartmental methods, with input values for dose level, dosing time, plasma concentration, and corresponding real-time values, based on drug dosing times whenever possible.

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

For area under the curve (AUC), samples below the limit of quantitation (BLQ) of the bioanalytical assays occurring prior to the achievement of the first quantifiable concentration will be assigned a concentration value of zero to prevent overestimation of the initial AUC. Samples that are BLQ at all other time points will be treated as missing data in WinNonlin. The nominal time point for a key event or dosing interval ($\tau$) 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 $AUC_{inf}$, $\lambda_z$ 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.

### 8.1.1. Pharmacokinetic Parameters

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

**Table 8-1. Study Treatments and Associated Analytes**

| Sequence | Treatment | Analyte |
|---|---|---|
| AB | **Treatment A:**<br>ATV<br>PRA/ROS<br>**Treatment B:**<br>FIL + ATV<br>FIL + PRA/ROS | ATV |
| | | 2-OH-ATV |
| | | PRA |
| | | ROS |
| BA | **Treatment B:**<br>FIL + ATV<br>FIL + PRA/ROS<br>**Treatment A:**<br>ATV<br>PRA/ROS | ATV |
| | | 2-OH-ATV |
| | | PRA |
| | | ROS |

The analytes and parameters presented in Table 8-2 will be used to evaluate the PK objectives of the study. The primary PK parameters are $AUC_{last}$, $AUC_{inf}$, and $C_{max}$ of ATV, 2-OH-ATV, PRA and ROS. Other PK parameters will be presented as applicable. The PK parameters to be estimated in this study are listed and defined in the Pharmacokinetic Abbreviations section.

**Table 8-2. Pharmacokinetic Parameters for Each Analyte**

| Matrix | Analyte | Parameters |
|---|---|---|
| Plasma | ATV | $AUC_{last}$, $AUC_{inf}$, $\%AUC_{exp}$, $C_{max}$, $C_{last}$, $T_{max}$, $T_{last}$, $\lambda_z$, CL/F, $V_z$/F and $t_{1/2}$, as applicable |
| | 2-OH-ATV | |
| | PRA | |
| | ROS | |

In addition, molar ratio of metabolite to parent exposure ($AUC_{last}$, $AUC_{inf}$, and $C_{max}$) will be calculated for individual subjects and summarized by treatment group of ATV alone and ATV + FIL.

- The 2-OH-ATV to ATV ratio for $AUC_{last}$ will be calculated by dividing the $AUC_{last}$ (in h*nmol/L) of 2-OH-ATV by the $AUC_{last}$ (in h*nmol/L) of ATV.
- The 2-OH-ATV to ATV ratio for $AUC_{inf}$ will be calculated by dividing the $AUC_{inf}$ (in h*nmol/L) of 2-OH-ATV by the $AUC_{inf}$ ((in h*nmol/L) of ATV.
- The 2-OH-ATV to ATV ratio for $C_{max}$ will be calculated by dividing the $C_{max}$ (in nmol/L) of 2-OH-ATV by the $C_{max}$ (in nmol/L) of ATV.

### 8.1.2. Statistical Analysis Method

#### 8.1.2.1. General Consideration

Individual subject concentration data and individual subject PK parameters for ATV, 2-OH-ATV, PRA and ROS will be listed and summarized using descriptive statistics by treatment. Summary statistics (numbers of subjects, mean, SD, coefficient of variation [%CV], median, minimum, maximum, Q1, and Q3) will be presented for both individual subject concentration data by time point and individual subject PK parameters by treatment. Moreover, the geometric mean, 95% confidence interval (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 lower limit of quantitation (LLOQ) for postdose time points.

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

The following tables will be provided for ATV, 2-OH-ATV, PRA and ROS by treatment:

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

The following figures will be provided for ATV versus ATV + FIL, and PRA/ROS versus PRA/ROS + FIL by treatment:

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

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

The following listings will be provided:

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

8.1.2.2. Statistical Methodology

8.1.2.2.1. 8.1.3.2.1 Analysis of Drug-Drug Interaction

An analysis of variance (ANOVA) using a mixed-effects model with treatment, period, and sequence as fixed effects and subject as a random effect will be fitted to the natural logarithmic transformation of PK parameters ($AUC_{last}$, $AUC_{inf}$, $C_{max}$) for ATV versus ATV + FIL, and PRA/ROS versus PRA/ROS+FIL. The same model will be fitted to the natural logarithmic transformation of molar ratio of metabolite to parent exposure (2-OH-ATV to ATV) of PK parameters ($AUC_{last}$, $AUC_{inf}$, and $C_{max}$) for ATV versus ATV + FIL. Additional analyses may be performed if useful and appropriate. Two-sided 90% CIs will be calculated for the ratios of geometric least-squares means (GLSMs) of primary PK parameters between test (Treatment B) versus reference (Treatment A) treatments.

Lack of PK interaction between the test and reference treatments will be concluded if the 90% CIs for the GLSM ratios are contained within the 70% - 143% range for ATV, 2-OH-ATV, PRA, and ROS AUC and $C_{max}$.

Treatment comparisons of interest are shown in Table 8-3.

**Table 8-3. Statistical Comparisons for Pharmacokinetic Analyses**

| Analyte | Parameter | Comparison (mean [%CV]) | | (% GLSM ratio and 90% CI) |
|---|---|---|---|---|
| | | Test | Reference | |
| ATV | $AUC_{last}$<br>$AUC_{inf}$<br>$C_{max}$ | ATV+FIL | ATV | Lack of effect boundary: 70% - 143% |
| 2-OH-ATV | | | | |
| PRA | | PRA/ROS+FIL | PRA/ROS | |
| ROS | | | | |
| Molar ratio of 2-OH-ATV to ATV | $AUC_{last}$ / $AUC_{last}$<br>$AUC_{inf}$/ $AUC_{inf}$<br>$C_{max}$ / $C_{max}$ | ATV+FIL | ATV | |

The statistical model will include treatment period and treatment sequence as a fixed effect and subject as a random effect. The following SAS PROC MIXED code will provide the treatment comparison analysis and the 90% CI calculations for natural log-transformed PK parameters.

```
proc mixed;
    where param='AUClast';
    class treat period sequence subjid;
    model lnest = treat period sequence / ddfm=kr;
    random subjid;
    lsmeans treat / diff cl alpha = 0.1;
    estimate 'Test versus Reference' 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 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}.

### 8.1.3. 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.

### 8.1.4. Changes From Protocol-Specified PK Analyses

Rather than 26 subjects (13 in each sequence), as specified in the protocol, 25 evaluable subjects (12 in one sequence and 13 in another sequence) was randomized and completed the study. The probability of the estimated two-sided 90% CI of the GLSM ratio of test versus reference treatments, with regards to $AUC_{inf}$, $AUC_{last,}$ and $C_{max}$, will be within [70%, 143%] changed from ≥ 85% to ≥ 83%.

# 9. REFERENCES

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

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

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

# 10. SOFTWARE

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

Phoenix WinNonlin® 8.2. Pharsight Corporation, Princeton, NJ, USA.

nQuery Version 8.5.2.0. Statistical Solutions, Cork, Ireland.

# 11. SAP REVISION

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

# 12. APPENDICES

## Appendix 1. Schedule of Assessments (Sequence AB)

| Study Procedure | Screening[a] | Admission Day −1 | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 7 | Day 8 | Day 9 | Day 10 | Day 11 | Day 12 | Day 13 | Day 14 | Day 15 | Day 16 | Discharge Day 17[b] | Follow-Up[c] Day 24 ± 2 | ET[d] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Written Informed Consent | X | | | | | | | | | | | | | | | | | | | | |
| Medical History | X | | | | | | | | | | | | | | | | | | | | |
| Complete Physical Examination | X | X | | | | | | | | | X | | | | | | | | X | | X |
| Symptom-Driven Physical Examination[e] | | | X | X | X | X | X | X | X | X | | X | X | X | X | X | X | X | | | |
| Height | X | | | | | | | | | | | | | | | | | | | | |
| Weight | X | X | | | | | | | X | | | | | | | X | | | X | | X |
| Vital Signs[f] | X | X | X | | X | | | X | X | | | X | | X | | X | X | | X | | X |
| HIV-1, HBV, and HCV Testing[g] | X | | | | | | | | | | | | | | | | | | | | |
| Hematology[g] | X | X | X | | X | | | X | X | | | | | X | X | X | X | | X | | X |
| Chemistry[g] | X | X | X | | X | | | X | X | | | | | X | X | X | X | | X | | X |
| Creatine phosphokinase (CPK) | X | X | X | | X | | | X | X | | | | | X | X | X | X | | X | | X |
| Calculated Creatinine Clearance | X | X | | | | | | | X | | | | | | | X | | | X | | X |

| Study Procedure | Screening[a] | Admission Day −1 | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 7 | Day 8 | Day 9 | Day 10 | Day 11 | Day 12 | Day 13 | Day 14 | Day 15 | Day 16 | Discharge Day 17[b] | Follow-Up[c] Day 24±2 | ET[d] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Urinalysis[g] | X | X | X | | X | | | X | X | | | | | X | X | X | X | | X | | X |
| Serum Pregnancy Test[g,h] | X | X | | | | | | | | | | | | | | | | | X | | X |
| Urine Pregnancy Test[h] | | X | | | | | | | X | | | | | | | | | | | | |
| Follicle-Stimulating Hormone (FSH)[g,h] | X | | | | | | | | | | | | | | | | | | | | |
| Thyroid Stimulating Hormone (TSH)[gh] | X | | | | | | | | | | | | | | | | | | | | |
| Urine Drug and Alcohol Screen[g] | X | X | | | | | | | | | | | | | | | | | | | |
| 12-Lead ECG | X | | | | | | | | | | | | | | | | | | | | |
| COVID-19 RT-PCR | X | X | | | | | | | | | | | | | | | | | | | |
| Randomization/ Enrollment[i] | | X | | | | | | | | | | | | | | | | | | | |
| Study Drug Administration[j] | | | X | | X | | | | X | X | X | X | X | X | X | X | X | X | X | | |
| Intensive Plasma PK[k] | | | X | | X | | | | | | | | | X | | X | | | | | |
| Genotype Testing[l] | | | X | | | | | | | | | | | | | | | | | | |

| Study Procedure | Screening[a] | Admission Day −1 | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 7 | Day 8 | Day 9 | Day 10 | Day 11 | Day 12 | Day 13 | Day 14 | Day 15 | Day 16 | Discharge Day 17[b] | Follow-Up[c] Day 24±2 | ET[d] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Review Study Restrictions | X | X | | | | | | | | | | | | | | | | | X | **X** | |
| Clinic Confinement | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | |
| Review AEs & Concomitant Medications[m] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |

AE = adverse event; ECG = electrocardiogram; COVID-19 RT-PCR = a real-time reverse transcription polymerase chain reaction (rTT-PCR) test for the qualitative detection of nucleic acid from SARS-CoV-2
eCRF = electronic case report form; ET = early termination; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV-1= human immunodeficiency virus type 1 and type 2; PE = physical examination; PG = pharmacogenomic; PK = pharmacokinetics

a. Prospective subject 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 17 (Sequence AB) following all assessments.
c. 7 (± 2) days after the last administration of study drug, all subjects will be contacted via telephone to review and document AEs and concomitant medications
d. Early termination (ET) assessments will be performed within 72 hours of prematurely discontinuing 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 body temperature.
g. See Protocol Section 6.6.5 for specifics.
h. Females of childbearing potential only.
i. On Day −1, subjects will be randomized the evening to receive 1 of 2 treatment sequences starting on Day 1.
j. See Protocol Section 5.4 for specifics.
k. Intensive PK sampling will occur relative to the morning dosing of study drug at the time points as outlined in Protocol Section 6.5.1.
l. Blood sample should be collected on Day 1, but may be collected at any time during the study, if necessary
m. 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. See Section 7, Adverse Events and Toxicity Management, for additional details.

## Appendix 2. Schedule of Assessments (Sequence BA)

| Study Procedure | Screening[a] | Admission Day −1 | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 7 | Day 8 | Day 9 | Day 10 | Day 11 | Day 12 | Day 13 | Day 14 | Day 15 | Day 16 | Day 17 | Day 18 | Day 19 | Day 20 | Day 21 | Day 22 | Discharge Day 23[b] | Follow-Up[c] Day 27 ± 2 | ET[d] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Written Informed Consent | X | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Medical History | X | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Complete Physical Examination | X | X | | | | | | | | | X | | | | | | | | | | | | | | X | | X |
| Symptom-Driven Physical Examination[e] | X | | X | X | X | X | X | X | X | X | | X | X | X | X | X | X | X | X | X | X | X | X | X | | | |
| Height | X | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Weight | X | X | | | | | | | X | | | | X | | | | | | | X | | | | | X | | X |
| Vital Signs[f] | X | X | X | | X | | | X | X | X | X | | X | | | | | | | X | | X | | | X | | X |
| HIV-1, HBV, and HCV Testing[g] | X | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Hematology[g] | X | X | X | | | | X | X | X | X | X | | X | | | | | | | X | | X | | | X | | X |
| Chemistry[g] | X | X | X | | | | X | X | X | X | X | | X | | | | | | | X | | X | | | X | | X |
| Creatine phosphokinase (CPK)[g] | X | X | X | | | | X | X | X | X | X | | X | | | | | | | X | | X | | | X | | X |
| Calculated Creatinine Clearance | X | X | | | | | | | X | | | | X | | | | | | | X | | | | | X | | X |
| Urinalysis[g] | X | X | X | | | | X | X | X | X | X | | X | | | | | | | X | | X | | | X | | X |
| Urine Pregnancy Test | | X | | | | | | | X | | | | | | | | | | | | | | | | | | |

| Study Procedure | Screening[a] | Admission Day –1 | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 7 | Day 8 | Day 9 | Day 10 | Day 11 | Day 12 | Day 13 | Day 14 | Day 15 | Day 16 | Day 17 | Day 18 | Day 19 | Day 20 | Day 21 | Day 22 | Discharge Day 23[b] | Follow-Upc Day 27 ± 2 | ETd |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Follicle-Stimulating Hormone (FSH)[gh] | X | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Thyroid Stimulating Hormone (TSH)[gh] | X | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Serum Pregnancy Testg,[h] | X | X | | | | | | | X | | | | | | | | | | | | | X | | | | | X |
| Urine Drug and Alcohol Screen[g] | X | X | | | | | | | | | | | | | | | | | | | | | | | | | |
| 12-Lead ECG | X | | | | | | | | | | | | | | | | | | | | | | | | | | |
| COVID-19 RT-PCR | X | X | | | | | | | | | | | | | | | | | | | | | | | | | |
| Randomization /Enrollment[i] | | X | | | | | | | | | | | | | | | | | | | | | | | | | |
| Study Drug Administration[j] | | | X | **X** | X | X | X | X | X | X | X | X | X | | | | | | | X | | X | | | | | |
| Intensive Plasma PK[k] | | | | | | | | X | | X | | | | | | | | | | X | | X | | | | | |
| Genotype Testing[l] | | | X | | | | | | | | | | | | | | | | | | | | | | | | |
| Review Study Restrictions | X | X | | | | | | | | | | | | | | | | | | | | | | | X | X | |
| Clinic Confinement | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | |

| Study Procedure | Screening[a] | Admission Day −1 | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 7 | Day 8 | Day 9 | Day 10 | Day 11 | Day 12 | Day 13 | Day 14 | Day 15 | Day 16 | Day 17 | Day 18 | Day 19 | Day 20 | Day 21 | Day 22 | Discharge Day 23[b] | Follow-Up[c] Day 27 ± 2 | ETd |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Review AEs & Concomitant Medications[m] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |

AE = adverse event; ECG = electrocardiogram; COVID-19 RT-PCR=a real-time reverse transcription polymerase chain reaction (rTT-PCR) test for the qualitative detection of nucleic acid from SARS-CoV-2
eCRF = electronic case report form; ET = early termination; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV-1 = human immunodeficiency virus type 1 and type 2; PE = physical examination; PG = pharmacogenomic; PK = pharmacokinetic(s); COVID-19 RT-PCR=a real-time reverse transcription polymerase chain reaction (rTT-PCR) test for the qualitative detection of nucleic acid from SARS-CoV-2

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 23 (Sequence BA) following all assessments.
c. 7 (± 2) days after the last administration of study drug, all subjects will be contacted via telephone to review and document AEs and concomitant medications.
d. Early termination (ET) assessments will be performed within 72 hours of prematurely discontinuing 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 body temperature.
g. See Protocol Section 6.6.5 for specifics.
h. Females of childbearing potential only.
i. On Day −1, subjects will be randomized the evening to receive 1 of 2 treatment sequences starting on Day 1.
j. See Protocol Section 5.4 for specifics.
k. Intensive PK sampling will occur relative to the morning dosing of study drug at the time points as outlined in Protocol Section 6.5.1.
l. Blood samples should be collected on Day 1, but may be collected at any time during the study, if necessary
m. 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. See Section 7, Adverse Events and Toxicity Management, for additional details.

# GS-US-417-5937_SAP

# ELECTRONIC SIGNATURES

| Signed by | Meaning of Signature | Server Date (dd-MMM-yyyy hh:mm:ss) |
|---|---|---|
| PPD | Clinical Pharmacology eSigned | 25-Feb-2021 21:51:56 |
| PPD | Project Team Leader eSigned | 25-Feb-2021 22:15:48 |
| PPD | Biostatistics eSigned | 26-Feb-2021 08:20:35 |