STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 1 Open-Label Study to Evaluate the Pharmacokinetics of Filgotinib in Subjects with Impaired Hepatic Function	
Study Phase:	1	
Name of Test Drug:	Filgotinib	
Study Number:	GS-US-417-4048	
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LIST OF ABBREVIATIONS

AE	adverse event
ANOVA	analysis of variance
BLQ	below the limit of quantitation
BMI	body mass index
CFR	Code of Federal Regulations
CI	confidence interval
CPT	Child-Pugh-Turcotte
CRF	case report form
CSR	clinical study report
CTCAE	Common Toxicity Criteria for Adverse Events
DMC	data monitoring committee
ECG	Electrocardiogram
eCRF	electronic case report form
ET	early termination
FU	follow-up
Gilead	Gilead Sciences
GLSM	geometric least-squares mean
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV, HIV-1	human immunodeficiency virus, type 1
HIV, HIV-2	human immunodeficiency virus, type 2
ID	Identification
LLOQ	lower limit of quantitation
LOQ	limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
PK	Pharmacokinetic(s)
PT	preferred term
Q1, Q3	first quartile, third quartile
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SE	standard error
SOC	system organ class
TEAE	treatment-emergent adverse events
TFLs	tables, figures, and listings
WHO	World Health Organization

PHARMACOKINETIC ABBREVIATIONS

λ_z	terminal elimination rate constant, estimated by linear regression of the terminal elimination phase of the log plasma/serum concentration of drug versus time curve of the drug
$\%AUC_{exp}$	percentage of AUC extrapolated between AUC_{last} and AUC_{inf}
AUC	area under the plasma/serum concentration versus time curve
AUC_{last}	area under the plasma/serum concentration versus time curve from time zero to the last quantifiable concentration
AUC_{inf}	area under the plasma/serum concentration versus time curve extrapolated to infinite time, calculated as $AUC_{last} + (C_{last}/\lambda_z)$
AUC_{x-xx}	partial area under the plasma/serum concentration versus time curve from time "x" to time "xx"
CL	Clearance
CL/F	apparent oral clearance after administration of the drug: $CL/F = Dose/AUC_{inf}$, where "Dose" is the dose of the drug
C_{last}	last observed quantifiable plasma/serum concentration of the drug
C_{max}	maximum observed plasma/serum concentration of drug
C_{min}	minimum observed plasma/serum concentration of drug
F	estimated oral bioavailability of the drug (%), calculated as $100(AUC_{oral} \times Dose_{iv})/(AUC_{iv} \times Dose_{oral})$
$t_{½}$	estimate of the terminal elimination half-life of the drug in plasma/serum, calculated by dividing the natural log of 2 by the terminal elimination rate constant (λ_z)
T_{last}	time (observed time point) of C_{last}
T_{max}	time (observed time point) of C_{max}
V_z	volume of distribution of the drug after intravenous administration
V_z/F	apparent volume of distribution of the drug

1. INTRODUCTION

This statistical analysis plan (SAP) describes the statistical analysis methods and data presentations to be used in tables, figures, and listings (TFLs) in the clinical study report (CSR) for Study GS-US-417-4048. This SAP is based on Protocol GS-US-417-4048 dated 12 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 pharmacokinetic (PK) of filgotinib and its metabolite, GS-829845 (formerly G254445), in subjects with impaired hepatic function relative to matched, healthy controls

The secondary objective of this study is as follows:

- To evaluate the safety and tolerability of filgotinib in subjects with normal and impaired hepatic function

1.2. Study Endpoints

The primary endpoints are PK parameters AUC_{last}, AUC_{inf}, and C_{max} for filgotinib and GS-829845.

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-417-4048 is an open-label, adaptive, single-dose Phase 1 study to evaluate the PK of filgotinib in subjects with impaired hepatic function. Up to 3 cohorts of subjects with hepatic impairment and their matched healthy controls are expected to enroll in this study.

- Cohort 1 (Moderate Hepatic Impairment): 20 subjects (10 subjects with moderate hepatic impairment and 10 healthy matched controls for 8 evaluable subjects per group).

- Adaptive Cohort 2 (Severe Hepatic Impairment): 20 subjects (10 subjects with severe hepatic impairment and 10 healthy matched controls for 8 evaluable subjects per group).

- Adaptive Cohort 3 (Mild Hepatic Impairment): 20 subjects (10 with mild hepatic impairment and 10 matched healthy controls for 8 evaluable subjects per group).

The extent of impairment is based on Child-Pugh-Turcotte (CPT) classification system. Class B in CPT system indicates moderate hepatic impairment for this study.

A subject with normal hepatic function may serve as a matched control across cohorts but may only serve as a matched control to one hepatic impaired subject within a cohort.

Subjects in adaptive Cohort 2 (Severe Hepatic Impairment) and Cohort 3 (Mild Hepatic Impairment) may be enrolled after the review of safety and PK data from subjects in Cohort 1 (Moderate Hepatic Impairment).

Following completion of Screening and Day -1 assessments, eligible subjects will be confined to the study center beginning Day -1 (one day before dosing) until the completion of assessments on Day 6. Subjects will return for an in-clinic follow-up (FU) visit on Day 15 (± 1 day).

A single dose of 100 mg filgotinib (1 x 100 mg tablet) will be administered in a fasted state on Day 1.

Pharmacokinetic Assessments

Intensive PK sampling will occur relative to dosing of filgotinib at the following time points:

Day 1: 0 (predose, ≤ 5 minutes prior to dosing), 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 18, 24, 36, 48, 72, 96, and 120 hours postdose

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

Protein Binding Assessment

Protein binding of filgotinib and GS-829845 will be assessed at or near their T_{max} timepoints as well as at another later time point.

Safety Assessments

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

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

- Complete physical exam: Screening, the FU visit or the ET visit (if applicable)
- Symptom driven physical exam: Days -1, 1, and every day during confinement
- Vital signs (blood pressure, heart rate, respiration rate, and body temperature): Screening, Days -1, 1, 3, 6, at the FU visit or the ET visit (if applicable)
- Height: Screening

- Weight: Screening and Day -1
- Clinical laboratory tests (hematology, blood chemistry, and urinalysis): Screening, Days -1, 1, 6 and the FU visit or the ET visit (if applicable)
- Urine drug, cotinine, and alcohol assessments: Screening, Day -1, and the FU visit or the ET visit (if applicable)
- 12-lead Electrocardiogram (ECG): Screening, Days -1, 1, 6, and the FU visit or the ET visit (if applicable)
- Serum Pregnancy Test (women of childbearing potential only): Screening, Days -1, 6, and the FU visit or the ET visit (if applicable)
- Serology Test (HBV, HCV[Ab; if positive, then reflex HCV RNA], HIV-1/2): Screening
- α-fetoprotein Test: Screening

1.4. Sample Size and Power

With 16 (8 per group) evaluable subjects, the estimated two-sided 90% CI of the geometric least-square mean (GLSM) ratio of test vs reference groups, with regards to PK parameters (AUC and C_{max}) would be within (50%, 200%) with over 95% probability, if the estimated GLSM ratio were 1.0. This is assuming the SDs for PK parameters between subjects within each group is no more than 0.347 (or 0.203) for the natural logarithm-transformed PK parameters for filgotinib (or GS-829845). Such assumptions are supported by PK data from a prior Gilead study of filgotinib (GS-US-417-3900) with 100 mg dose in healthy volunteers.

An overage of 2 subjects per group will be enrolled in order to accommodate subject drop-outs, so a total sample size of 20 subjects (10 per group) for each cohort will be required.

2. TYPE OF PLANNED ANALYSIS

2.1. Data Monitoring Committee Analyses

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

2.2. Interim Analysis

No interim analysis is planned.

2.3. Final Analysis

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

2.4. Changes from Protocol-Specified Analysis

No changes from protocol-specified analyses are planned.

3. GENERAL CONSIDERATIONS FOR DATA ANALYSES

Analysis results will be presented using descriptive statistics. For categorical variables, the number and percentage of subjects in each category will be presented; for continuous variables, the number of subjects (n), mean, 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 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 safety listings.

3.1.2. Safety Analysis Set

The Safety Analysis Set includes all subjects who took study drug. This is the primary analysis set for safety tables.

3.1.3. Pharmacokinetic Analysis Sets

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 enrolling subjects. No covariates will be included in the analyses.

3.3. Examination of Subject Subsets

There are no prespecified subject subsets for analyses.

3.4. Multiple Comparisons

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

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 randomization 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, and Treatment Day

Predose value is defined as the last available off-treatment value collected prior to the 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 the study drug 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 Visit Windows

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

- An unscheduled visit prior to the first dose of study drug may be included in the calculation of predose value, if applicable.
- For subjects who discontinue from the study, ET data will be summarized as a separate visit, labeled 'Early Termination'.

The predose and postdose visits for laboratory tests and vital signs are summarized in Table 3-1, Table 3-2, and Table 3-3, respectively.

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

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

Table 3-2. Predose and Postdose Visits for Vital Signs

Visit Label	Study Day and Time Point
Predose	1
Day 3	3
Day 6	6
Follow-up	15 (±1)
Early Termination	Early Termination (if applicable)

Table 3-3. Predose and Postdose Visits for ECG

Visit Label	Study Day and Time Point
Predose	-1
Day 1	1 (2 hours post dose)
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 values:
  - The record closest to the nominal day for that visit will be selected.
  - If there are 2 records that are equidistant from the nominal day, the later record will be selected.
  - If there is more than 1 record on the selected day, the average will be taken, unless otherwise specified.

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

- For predose, the last available record on or prior to the date and time of the first dose of study drug will be selected. If there are multiple records with the same time or no time recorded on the same day, the value with the lowest severity will be selected (eg, normal will be selected over abnormal for safety ECG findings).
- For postdose values, 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 hepatic function group and overall. This summary will present the number of subjects enrolled, and the number and percentage of subjects in each of the categories listed below. For the Safety Analysis Set category, the denominator for the percentage calculation will be the total number of subjects enrolled for each column. For all other categories, the denominator for the percentage calculation will be the total number of subjects in the Safety Analysis Set for each column.

- Safety Analysis Set
- PK Analysis Set for each analyte
- Completed study drug
- Did not complete study drug with reasons for premature discontinuation of study drug, as applicable
- Completed the study
- Did not complete the study with reasons for premature discontinuation of study, 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 hepatic 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.

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 will be listed.

4.3. Protocol Deviations for Eligibility

A by-subject listing will be provided for the enrolled subjects who failed to meet at least 1 inclusion criterion 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.

5. BASELINE CHARACTERISTICS

5.1. Demographics

Subject demographic variables (ie, age, sex, race, and ethnicity) will be summarized by hepatic 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. Other Baseline Characteristics

Other baseline characteristics include body weight (in kg), height (in cm), body mass index (BMI; in kg/m^2), and creatinine clearance (in mL/min) by Cockcroft-Gault method. These baseline characteristics will be summarized by hepatic function group and overall using descriptive statistics for continuous variables and using number and percentage of subjects for categorical variables. For baseline body weight, height, BMI, and creatinine clearance, 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 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 "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 procedure will be considered related to study procedure for summary purposes. However, by-subject data listings will show the relationship as missing from that captured on the CRF.

7.1.5. Serious Adverse Events

Serious adverse events (SAEs) will be identified and captured as SAEs if the AEs met the definition of SAEs that 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 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 hepatic 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 TEAEs leading to study discontinuation

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

Multiple events will be counted only once per subject in each summary. Adverse events will be summarized and listed first in alphabetic order of SOC and then by PT in descending order of total frequency within each SOC. For summaries by severity, the 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 based on protocol specified severity grading will be flagged in the data listings, as appropriate.

No formal statistical testing is planned for laboratory assessments.

7.2.1. Summaries of Numeric Laboratory Results

Descriptive statistics will be provided by hepatic 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 as specified in study protocol 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 the 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 hepatic 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 hepatic function group for vital signs (including body temperature, pulse rate, respiratory rate, systolic and diastolic blood pressure) as follows:

- 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 formal 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 hepatic function group using the following categories: normal, abnormal, not clinically significant; abnormal, clinically significant; or missing. The number and percentage of subjects in each cross-classification group of the shift table will be presented. Subjects with a missing value at predose or postdose will not be included in the denominator for percentage calculation. No formal statistical testing is planned.

A by-subject listing for ECG assessment results will be provided by subject ID number and 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 deviations from the protocol-specified safety analyses.

8. PHARMACOKINETIC EVALUATION/ANALYSIS

8.1.1. 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 LLOQ 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.

8.1.2. Pharmacokinetic Parameters

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

Table 8-1. Study Treatment and Associated Analytes

Treatment	Analyte
Single dose of 100 mg filgotinib (1 x 100 mg tablet) in fasted state	Filgotinib and GS-829845

Pharmacokinetic 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 filgotinib and GS-829845. The PK parameters to be estimated in this study are listed and defined in the Pharmacokinetic Abbreviations section.

Table 8-2. Pharmacokinetic Parameters for Each Analyte

Analyte	Parameters
Filgotinib	AUC_{last}, AUC_{inf}, $\%AUC_{exp}$, C_{max}, T_{max}, C_{last}, T_{last}, λ_z, $t_{1/2}$, CL/F, V_z/F, as applicable
GS-829845	AUC_{last}, AUC_{inf}, $\%AUC_{exp}$, C_{max}, T_{max}, C_{last}, T_{last}, λ_z, $t_{1/2}$, as applicable

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 hepatic function group. The GS-829845 to figotinib ratio for AUC_{last} will be calculated by dividing the AUC_{last} (in h*nmol/L) of GS-829845 by the AUC_{last} (in h*nmol/L) of filgotinib. The GS-829845 to figotinib ratio for AUC_{inf} will be calculated by dividing the AUC_{inf} (in h*nmol/L) of GS-829845 by the AUC_{inf} ((in h*nmol/L) of filgotinib. The GS-829845 to figotinib ratio for C_{max} will be calculated by dividing the C_{max} (in nmol/L) of GS-829845 by the C_{max} (in nmol/L) of filgotinib.

8.1.3. Statistical Analysis Methods

8.1.3.1. General Considerations

Individual subject concentration data and individual subject PK parameters including percentage of protein binding for filgotinib and GS-829845 will be listed and summarized using descriptive statistics by hepatic 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 treatment. Moreover, the geometric mean, 95% CI, and the mean and SD of the natural log-transformed values will be presented for individual subject PK parameter data.

Individual concentration data listings and summaries will include all subjects with concentration data. The sample size for each time point will be based on the number of subjects with nonmissing concentration data at that time point. The number of subjects with concentration BLQ will be presented for each time point. For summary statistics, BLQ values will be treated as 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.

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

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

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

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

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

The following listings will be provided:

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

8.1.3.2. Statistical Methodology

The statistical comparisons of the natural log-transformed PK parameters for each analyte between hepatic impaired subjects and healthy controls will be based on the PK Analysis Set for the analyte under evaluation. For each analyte, all subjects with available data for the PK parameter under evaluation will be included in the modeling.

Comparisons of interest are shown in Table 8-3**.**

Table 8-3. Statistical Comparisons for Pharmacokinetic Analyses

Analyte	Parameter	Comparison	
		Test	**Reference**
Filgotinib	AUC_{last}	Moderately impaired hepatic function	Normal hepatic function
	AUC_{inf}		
	C_{max}		
	AUC_{last}	Severely impaired hepatic function	Normal hepatic function
	AUC_{inf}		
	C_{max}		
	AUC_{last}	Mildly impaired hepatic function	Normal hepatic function
	AUC_{inf}		
	C_{max}		
GS-829845	AUC_{last}	Moderately impaired hepatic function	Normal hepatic function
	AUC_{inf}		
	C_{max}		
	AUC_{last}	Severely impaired hepatic function	Normal hepatic function
	AUC_{inf}		
	C_{max}		
	AUC_{last}	Mildly impaired hepatic function	Normal hepatic function
	AUC_{inf}		
	C_{max}		

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

The statistical model will include hepatic function group as a fixed effect.

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

```
proc mixed;
  by analyte paramcd;
  class subjid hepaticgrp;
  model lnest = hepaticgrp / ddfm = kr;
  repeated / group = hepaticgrp
  lsmeans hepaticgrp / e diff cl alpha = 0.1;
  estimate 'Impaired versus Normal' hepaticgrp 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 one-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 filgotinib and GS-829845.

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

To evaluate the protein binding of filgotinib and GS-829845, the percent of unbound filgotinib and GS-829845 at T_{max} and a later time point will be summarized by time point and hepatic function group. Protein binding data for individual subject will be presented in a listing.

For subjects with hepatic impairment, the relationship between plasma PK exposure parameters (AUC_{last}, AUC_{inf} and C_{max}) and overall CPT impairment score may be explored using Spearman correlation analysis and examined graphically. The relationship between the PK parameters

(AUC_{last}, AUC_{inf} and C_{max}) and baseline lab tests (albumin, total bilirubin, prothrombin time, and International Normalized Ratio [INR]) will be also explored using Spearman correlation analysis and examined graphically for hepatic impaired subjects and for all subjects by hepatic function group.

8.1.4. Sensitivity Analysis

Sensitivity analysis will be conducted for the key PK analyses if the PK scientist identifies PK data as questionable.

The natural log-transformed values of plasma PK parameters AUC_{last}, AUC_{inf} and C_{max} will be used to assess potential outliers. For any specific PK parameter (AUC_{last}, AUC_{inf} or C_{max}) of any analyte (filgotinib or GS-829845), the mean of log-transformed parameter values minus 2 times of SD of log-transformed values from all evaluable subjects will be used as the lower bound, while the mean plus 2 times of SD of log-transformed values from all evaluable subjects will be used as the upper bound. Log-transformed values of a specific PK parameter below the lower bound or above the upper bound will be marked as potential data outliers for this PK parameter. Any subject with log-transformed parameter values being marked as potential data outliers for all PK parameters AUC_{last}, AUC_{inf} and C_{max} for both filgotinib and GS-829845 will be marked as a potential outlying subject.

The sensitivity analaysis will include all data excluding ones from the potential outlying subjects. This sensitivity analysis will be denoted as secondary analysis in the TFLs, while the analysis using all data from PK Analysis Sets will be denoted as primary analysis. The sensitivity analysis will consist of the PK parameter summary tables and the tables and listings for statistical comaprisons between the hepatic function groups for both filgotinib and GS-829845.

9. REFERENCES

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

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

10. SOFTWARE

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

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

nQuery Advisor(R) Version 6.0. 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

Study Procedure	Screen[a]	Day -1	Day 1	Days 2-5	Day 6[b]	Day 15 (± 1 day)[c]	ET[d]
Written Informed Consent	X						
Medical History	X						
Complete Physical Exam	X					X	X
Symptom-Driven Physical Examination[e]		X	X	X	X		
Height	X						
Weight, BMI	X	X					
Vital Signs[f]	X	X	X	X[g]	X	X	X
HIV-1/2, HBV, and HCV Testing	X						
Hematology[h]	X	X[i]	X		X	X	X
Chemistry[h]	X	X[i]	X		X	X	X
Coagulation[h]	X	X[i]	X		X	X	X
α-fetoprotein	X						
Urinalysis	X	X[i]	X		X	X	X
Serum Pregnancy Test[j]	X	X[i]			X	X	X
FSH[k]	X						
Urine Drug, Cotinine, and Alcohol Screen	X	X[i]				X	X
12-Lead ECG	X	X	X[l]		X	X	X
Enrollment[m]			X				
Study Drug Administration			X				
PK Assessments[n]			X				X
Review Study Restrictions	X	X			X	X	X
Clinic Confinement		X					
Review AEs & Concomitant Medications[o]	X						

a Prospective subjects should be screened no more than 28 days prior to administration of the first dose of study drug.
b Subjects will be discharged from the clinic on Day 6, following all morning assessments.

c Subjects will return for a FU visit on Day 15 (± 1 day).
d Assessments will be performed within 72 hours of early termination (ET) 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 Day 3 only.
h Hematology, Chemistry, Coagulation: as specified in study protocol.
i Two sets of safety labs will be collected upon clinic admission; one will be sent to the central lab and another will be sent to the sites' local lab to obtain results in time for enrollment on Day 1.
j Females of child-bearing potential only.
k Female subjects ≤ 54 years old with amenorrhea > 12 months.
l 2 hours postdose.
m On Day 1, subjects will be enrolled immediately prior to dosing.
n Intensive PK sampling will occur relative to dosing of filgotinib on Day 1 at the following time points for each cohort: Day 1: 0 (predose, ≤ 5 min before dose), 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 18, 24, 36, 48, 72, 96, and 120 hours postdose. A blood sample for PK analysis will be collected at the ET visit (if applicable) and may be analyzed.
o From the time of obtaining informed consent through the first administration of study drug, record all SAEs, as well as any nonserious AEs related to protocol-mandated procedures on the AE 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 Adverse Events and Toxicity Management in study protocol for additional details.

GS-US-417-4048 SAP

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Clinical Pharmacology eSigned	20-Dec-2018 16:18:15
PPD	Biostatistics eSigned	20-Dec-2018 22:21:16
PPD	Clinical Research eSigned	20-Dec-2018 22:34:38