STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 1b Open-Label Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Idelalisib in Subjects Receiving Ruxolitinib as Therapy for Primary, Post-Polycythemia Vera, or Post-Essential Thrombocythemia Myelofibrosis with Progressive or Relapsed Disease
Name of Test Drug:	Idelalisib
Study Number:	GS-US-397-1245
Protocol Version (Date):	Amendment 5 (26 October 2016)
Analysis Type:	Final
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Analysis Plan Author(s):	PPD

CONFIDENTIAL AND PROPRIETARY INFORMATION

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LIST OF ABBREVIATIONS

AE	adverse event
AEI	adverse event of interest
ALT	alanine aminotransferase
ALP	alkaline phosphatase
AST	aspartate aminotransferase
BID	twice per day
BLQ	below the limit of quantitation
CI	confidence interval
CLL	chronic lymphocytic leukemia
CMV	cytomegalovirus
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DMC	data monitoring committee
ECG	electrocardiogram
eCRF	electronic case report form
ELN	European Leukemia Net
EOT	end of treatment
EOS	end of study
FAS	Full Analysis Set
HLGT	high level group term
HLT	high level term
iNHL	indolent non-Hodgkin lymphoma
IWG-MRT	International Working Group for Myeloproliferative Neoplasms Research and Treatment
LLT	lower level term
LOQ	limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
PK	pharmacokinetics
PJP	*Pneumocystis jirovecii* pneumonia
PMF	primary myelofibrosis
PML	progressive multifocal leukoencephalopathy
post-ET MF	Post-Essential Thrombocythemia Myelofibrosis
post-PV MF	Post-PolycythemiaVera Myelofibrosis
PT	preferred term
Q1, Q3	first quartile, third quartile
SAE	serious adverse event
SAP	statistical analysis plan
SE	standard error
SI (units)	international system of units

SOC	system organ class
SRT	safety review team
StD	standard deviation
TEAE	treatment-emergent adverse event
TFLs	tables, figures, and listings
ULN	upper limit of normal
WHO	World Health Organization

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-397-1245. This SAP is based on Protocol GS-US-397-1245 Amendment 5 dated 26 October 2016 and the electronic case report form (eCRF). This SAP will be finalized before database finalization. Any changes made after finalization of the SAP will be documented in the CSR.

Following internal review, Gilead Sciences, Inc. (Gilead) decided to cease clinical development of idelalisib in new indications which included terminating Study GS-US-397-1245. A total of 10 subjects had been enrolled when the study was terminated.

1.1. Study Objectives

The primary objectives of this study are as follows:

- To evaluate the safety and tolerability of idelalisib through 28 days in subjects receiving ruxolitinib as therapy for intermediate- to high-risk primary myelofibrosis (PMF), post-polycythemia vera, or post-essential thrombocythemia myelofibrosis (post-PV MF or post-ET MF) with progressive or relapsed disease

- To determine the pharmacokinetics (PK) of idelalisib and ruxolitinib in subjects receiving ruxolitinib with PMF, post-PV MF, or post-ET MF with progressive or relapsed disease

The secondary objectives of this study are as follows:

- To evaluate the safety and tolerability of continuous daily administration of idelalisib beyond 28 days in subjects receiving ruxolitinib with PMF, post-PV MF, or post-ET MF

- To evaluate the efficacy of idelalisib in subjects receiving ruxolitinib with PMF, post-PV MF, or post-ET MF by 2013 Revised International Working Group for Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) and European Leukemia Net (ELN) response criteria

CCI [redacted]

1.2. Study Design

This is a Phase 1b, open-label, dose escalation study. The planned number of subjects in each cohort is 6. There will be 4 cohorts (A, B, C, and D), which will be enrolled sequentially (Figure 1). Cohort A will be enrolled first.

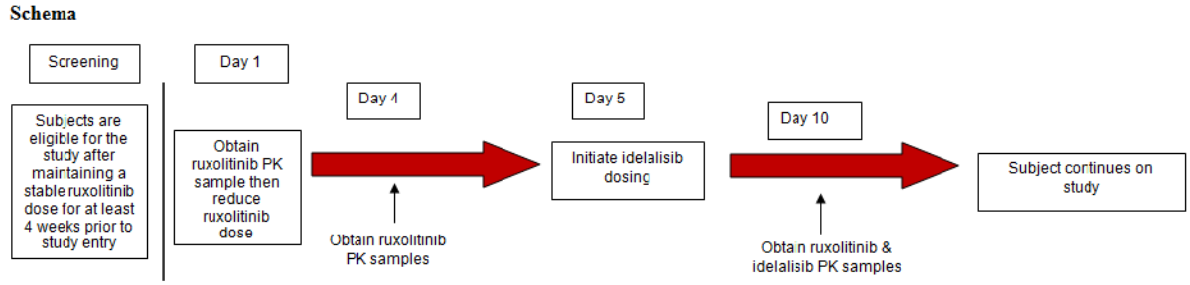
Idelalisib will be administered in subjects receiving ruxolitinib as therapy for PMF, post-PV MF, or post-ET MF, and who have been maintained on a stable dose of ruxolitinib for at least 4 weeks prior to study entry. On Day 1 subjects will have a PK sample drawn and then the ruxolitinib dose will be reduced as follows:

- Subjects on a stable ruxolitinib dose of greater than or equal to 10 mg twice daily, will have their ruxolitinib dose reduced by 50% (rounded up to the closest available tablet strength).
- Subjects on a stable ruxolitinib dose of 5 mg twice daily, will have their ruxolitinib dose reduced to 5 mg once daily.

Idelalisib will be administered starting on Day 5.

PK samples will be obtained on Days 1, 4 and 10 as shown in the schema below:

Figure 1. PK Schema



The starting doses of idelalisib in Cohorts A, B, C, and D are 50 mg once daily, 50 mg twice daily, 150 mg once daily, and 150 mg twice daily, respectively. Enrollment into the study will be on hold while the safety review team (SRT) evaluates the data prior to cohort expansion and dose escalation.

The first 3 subjects will be enrolled in Cohort A at 50 mg once daily idelalisib. After the third subject has completed Day 28 (4 weeks), the SRT will review the safety data. Enrollment will be on hold until the SRT determines the cohort can be expanded to enroll an additional 3 subjects. After the sixth subject in Cohort A completes Day 56 (8 weeks), the SRT will review the cumulative safety and PK data from all subjects in Cohort A. Enrollment will be on hold until the SRT determines Cohort B can be open to enrollment. If the SRT deems the combination of idelalisib with ruxolitinib safe and tolerable at the 50 mg once daily dose, Cohort B will be open to enrollment.

Enrollment and safety assessment by the SRT in Cohort B at 50 mg twice daily idelalisib will proceed as follows: The first 3 subjects will be enrolled. After the third subject has completed Day 28 (4 weeks), the SRT will review the cumulative safety data for Cohorts A and B. Enrollment will be on hold until the SRT determines Cohort B can be expanded to enroll an additional 3 subjects. After the sixth subject in Cohort B completes Day 28 (4 weeks), the SRT

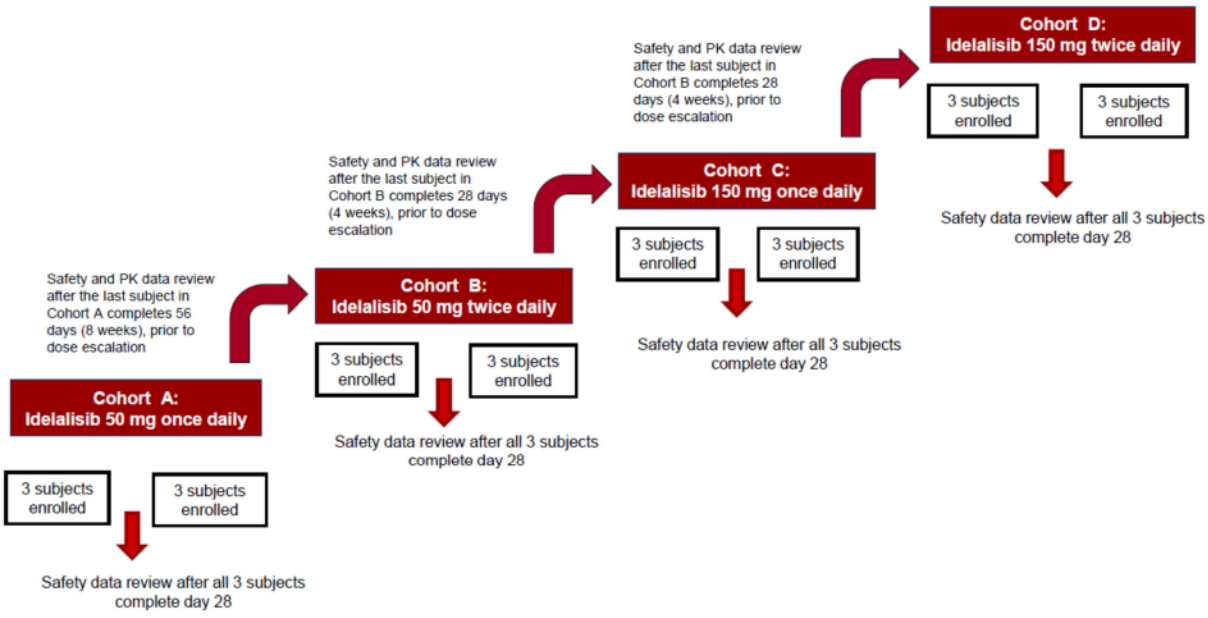
will review the cumulative safety data from all subjects in Cohorts A and B, and the cumulative PK data for Cohort B. Enrollment will be on hold until the SRT determines Cohort C can be open to enrollment.

If the SRT determines subsequent cohorts can be enrolled, Cohorts C and D will proceed sequentially in a similar manner as Cohort B with a 150 mg once daily or 150 mg twice daily idelalisib dose, respectively.

Additional cohorts are not planned after enrollment in Cohort D is complete. Subjects who do not receive ≥ 1 dose of idelalisib will be deemed unevaluable and replaced.

In subjects without demonstrable clinical benefit, dose escalation (to a higher dose cohort) may be permitted by the SRT after Cohort C (idelalisib 150 mg once daily) has been fully enrolled and the last subject has been on study drug for at least 28 days.

Figure 2. Study Schema



1.3. Study Duration

As previously described, Gilead decided to terminate this study following an internal decision to cease clinical development of idelalisib in new indications. The overall duration of the trial was initially planned to be approximately 3 years, with no long-term follow-up evaluations planned after that point. The actual duration of the study is approximately 2.5 years.

1.4. Sample Size and Power

A total of 10 subjects had been enrolled when the study was terminated.

The following describes the original sample size and power consideration:

As this is a Phase 1b study with a primary objective of assessing safety, the sample size is not based on formal power calculations. The sample size of approximately 6 subjects per dose cohort in Cohorts A, B, C, and D is considered adequate for an initial assessment of safety and tolerability for subsequent evaluations.

2. TYPE OF PLANNED ANALYSIS

2.1. Interim Analyses

This study does not have a DMC. Therefore, no analyses will be conducted for the DMC.

The safety review team will review and evaluate the safety and PK data of idelalisib with ruxolitinib prior to cohort expansion and dose escalation.

2.2. Final Analysis

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

3. GENERAL CONSIDERATIONS FOR DATA ANALYSES

Analysis results will be presented using descriptive statistics. For categorical variables, the number and percentage of subjects in each category will be presented; for continuous variables, the number of subjects (n), mean, standard deviation (StD) 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 ID number, visit date, and time (if applicable). Data collected on log forms, such as AEs, will be presented in chronological order within the 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.

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

3.1.1. All Enrolled Analysis Set

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

3.1.2. Full Analysis Set

The Full Analysis Set (FAS) includes all subjects who took at least 1 dose of study drug.

3.1.3. Pharmacokinetic Analysis Set

The Pharmacokinetic Analysis Set will include all enrolled subjects who took at least 1 dose of study drug and have at least 1 nonmissing postdose value reported by the PK laboratory. This is the primary analysis set for all PK analyses.

3.2. Subject Grouping

For analyses based on the FAS, subjects will be grouped according to the actual treatment received.

For the PK Analysis Set, subjects will be grouped according to the actual treatment they received.

3.3. Strata and Covariates

This study does not use a stratified randomization schedule when enrolling subjects.
No covariates will be included in safety analyses.

3.4. Examination of Subject Subgroups

There are no prespecified subject subgroupings for safety analyses.

3.5. Multiple Comparisons

Adjustments for multiplicity will not be made, because no formal statistical testing will be performed in this study.

3.6. Missing Data and Outliers

3.6.1. Missing Data

In general, missing data will not be imputed unless methods for handling missing data are specified.

3.6.2. Outliers

All data will be included in the data analysis.

3.7. Data Handling Conventions and Transformations

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

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

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

- If at least 1 subject has a concentration value of BLQ for the time point, the minimum value will be displayed as "BLQ."

- If more than 25% of the subjects have a concentration data value of BLQ for a given time point, the minimum and Q1 values will be displayed as "BLQ."

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

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

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

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

3.8. Analysis Visit Windows

3.8.1. Definition of Study Day

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

- For postdose study days: Assessment Date – First Dosing Date + 1

- For days prior to the first dose: Assessment Date – First Dosing Date

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

3.8.2. Analysis Visit Windows

For parameters that will be summarized by visit, the nominal visit as recorded on the eCRF will be used. For parameters assessed at the end of study (EOS) visit, the assessment results will be assigned to the next scheduled visit where the respective data were scheduled to be collected. There will be no additional analysis windowing done based on the assessment date. Unscheduled visits prior to the first dose date will be included for the calculation of baseline values.

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

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

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

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

- For postbaseline values:

  — The record closest to the nominal day 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.

4. SUBJECT DISPOSITION

4.1. Subject Enrollment and Disposition

A summary of subject disposition will be provided by dose level cohort. This summary will present the number of subjects screened, the number of subjects enrolled, and the number of subjects in each of the categories listed below:

- Full Analysis Set
- Completed idelalisib dosing through Week 24
- Completed ruxolitinib dosing through Week 24
- Discontinued idelalisib with reasons for premature discontinuation
- Discontinued ruxolitinib with reasons for premature discontinuation
- Completed study
- Discontinued the study with reasons for premature discontinuation of study

For the status of study drug and study completion and reasons for premature discontinuation, the number and percentage of subjects in each category will be provided. The denominator for the percentage calculation will be the total number of subjects in the FAS corresponding to that column.

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

- Reasons for premature study drug or study discontinuation

4.2. Extent of Study Drug Exposure and Adherence

4.2.1. Duration of Exposure to Study Drug

Duration of exposure to idelalisib will be defined as (last idelalisib dosing date – first idelalisib dosing date + 1), regardless of temporary interruptions in study drug administration, and will be expressed in months using up to 1 decimal place (eg, 2.5 months). Duration of exposure to idelalisib will be summarized using descriptive statistics and as the number and percentage of subjects exposed for at least 1 day, 2, 4, 6, and 12 months, and every 6 months thereafter.

Number and percentage of subjects who had idelalisib dose interruption, reduction, and re-escalation will be summarized. Idelalisib dosing records and drug accountability (dispense and return) records will be listed by subject.

Duration of exposure to ruxolitinib will be defined as (last ruxolitinib dose date - first ruxolitinib dose date + 1) and will be summarized using descriptive statistics and as the number and percentage of subjects exposed for at least 1 day, 2, 4, 6, and 12 months, and every 6 months thereafter.

4.2.2. Adherence to Study Drug

Adherence (%) with idelalisib will be calculated as:

Adherence (%) = (sum of pills dispensed minus pills returned) divided by (sum over all dosing period of [total daily pills x dosing duration]), taking into account investigator-prescribed interruption, reductions, and escalations.

Descriptive statistics for adherence along with the number and percentage of subjects belonging to adherence categories (eg, $< 75\%$ or $\geq 75\%$) will be provided.

A separate by-subject listing of study drug administration and drug accountability will be provided by subject ID number (in ascending order) and visit (in chronological order).

4.3. Protocol Deviations

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

5. BASELINE CHARACTERISTICS

5.1. Demographics

Subject demographic variables (ie, age, sex, race, and ethnicity) will be summarized by 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 FAS.

A by-subject demographic listing 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), and body mass index (BMI; in kg/m^2). These baseline characteristics will be summarized 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 FAS.

A by-subject listing of other baseline characteristics will be provided by subject ID number in ascending order.

5.3. Medical History

Medical history will be collected at screening for general conditions (ie, conditions not specific to the disease being studied).

General medical history data will not be coded, but will be listed only.

A by-subject listing of general medical history including conditions with start and stop dates will be provided by subject ID number in ascending order.

5.4. Disease History

Number and percentage of subjects with type of cancer, scoring system and rist at diagnosis, scoring system and rist at screening, and JAK status assessment will be summarized using summary statistics for categorical variables.

Time since diagnosis will be summarized by using summary statistics for continuous variables.

Time since diagnosis (years) will be calculated as (date of first dose of study drug – date of diagnosis)/365.25.

All disease history with partial diagnosis date will be identified and the partial dates will be imputed as follows:

- If day and month are missing but year is available, then the imputed day and month will be 01 Jan.
- If day is missing but the month and year are available, then the imputed day will be the first day of the month.

No imputation will be done if the year of diagnosis is missing.

A by-subject listing of disease history and status will be provided by subject ID number in ascending order.

5.5. Prior Anticancer Therapy and Prior Radiation

For prior therapy, number of prior regimens and time since the completion of last regimen will be summarized by dose level cohort using descriptive statistics based on the FAS. A partial completion date will be imputed as follows:

- If day and month are missing but year is available, then the imputed day and month will be 01 Jan.
- If day is missing but the month and year are available, then the imputed day will be the first day of the month.
- Partial date will not be imputed if the year is missing.

The regimens and prior therapies that the subjects received will be summarized. The last regimen subjects received prior to study entry and the best response to the last regimen will be summarized.

Number of subjects who received prior and on-study radiation therapy will be listed.

6. EFFICACY ANALYSES

Due to the early termination of the study, the prespecified efficacy analyses cannot be conducted.

7. SAFETY ANALYSES

Safety data will be described and summarized for the first 28 days of idelalisib administration and over the entire idelalisib treatment period.

7.1. Adverse Events and Deaths

7.1.1. Adverse Event Dictionary

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

7.1.2. Adverse Event Severity

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

7.1.3. Relationship of Adverse Events to Study Drug

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

7.1.4. Serious Adverse Events

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

7.1.5. Treatment-Emergent Adverse Events

7.1.5.1. Definition of Treatment-Emergent Adverse Events

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

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

7.1.5.2. Incomplete Dates

All AEs with partial onset or stop dates will be identified and the partial dates will be imputed as follows:

- For AE onset date: If day and month are missing but year is available, then the imputed day and month will be 01 Jan or the first dosing date if they have the same year, whichever is later. If day is missing but the month and year are available, then the imputed day will be the first day of the month or the first dosing date if they have the same month and year, whichever is later.

- For AE stop date: If day and month are missing but year is available, then the imputed day and month will be 31 Dec of that year. If day is missing but the month and year are available, then the imputed day will be the last day of the month or death date, whichever is earlier.

Imputed AE onset date should be on or before the AE stop date. In few circumstances where AE stopped before the first dosing date and the imputed AE onset date becomes later than AE stop date, AE start date will be set to AE stop date.

7.1.6. Summaries of Adverse Events and Deaths

Treatment-emergent AEs will be summarized based on the FAS.

7.1.6.1. Summaries of AE Incidence by Severity

The number and percentage of subjects who experienced at least 1 TEAE will be provided and summarized by SOC, PT, and dose level cohort. For other AEs described below, summaries will be provided by SOC, PT, maximum severity, and dose level cohort:

- TEAEs
- TEAEs of Grade 3 or higher
- TE idelalisib-related AEs
- TE ruxolitinib-related AEs
- TE idelalisib-related AEs of Grade 3 or higher
- TE ruxolitinib-related AEs of Grade 3 or higher
- TE SAEs
- TE idelalisib-related SAEs
- TE ruxolitinib-related SAEs

- TEAEs leading to premature discontinuation of idelalisib
- TEAEs leading to death
- TEAEs leading to temporary interruption of idelalisib
- TEAEs leading to dose reduction of idelalisib

A brief, high-level summary of AEs described above will be provided by dose level cohort and by the number and percentage of subjects who experienced the above AEs.

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

In addition to the above summary tables, all TEAEs will be summarized by PT only, in descending order of total frequency.

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

- All AEs, indicating whether the event is treatment emergent
- All AEs of Grade 3 or higher
- SAEs
- Deaths
- AEs leading to death
- AEs leading to interruption, reduction and premature discontinuation of idelalisib

7.1.7. Treatment-Emergent Adverse Events of Interest

The treatment-emergent AEs of interest (AEI) include:

- ≥ Grade 3 diarrhea/colitis
- ≥ Grade 3 rash in Medical Search Term (terms are defined in Appendix 2 of this SAP.)
- Any grade pneumonitis
- Any grade organizing pneumonia
- Any grade bowel perforation
- Any grade progressive multifocal leukoencephalopathy (PML)

- ≥ Grade 3 febrile neutropenia
- ≥ Grade 3 infection
- Any grade *Pneumocystis jirovecii* pneumonia (PJP)
- Any grade cytomegalovirus (CMV) infection

Table 1. Grouped Terms for Adverse Events of Interest

AEI	Grouped Terms
Diarrhea/colitis	PT: Diarrhoea or colitis
Pneumonitis	PT: Pneumonitis
Organizing pneumonia	PT: Organizing pneumonia
Febrile neutropenia	PT: Febrile neutropenia
PML	PT: Progressive multifocal leukoencephalopathy
Infection	SOC: Infections and infestations or PT: Febrile neutropenia
PJP	HLT: Pneumocystis infections
CMV	HLT: Cytomegaloviral infections or PT: Cytomegalovirus test positive
Bowel perforation	Following terms based on PT: Rectal perforation Duodenal perforation Duodenal ulcer perforation Duodenal ulcer perforation, obstructive Diverticular perforation Gastrointestinal perforation Gastrointestinal ulcer perforation Appendicitis perforated Ileal perforation Ileal ulcer perforation Intestinal perforation Intestinal ulcer perforation Jejunal perforation Jejunal ulcer perforation Large intestinal ulcer perforation Large intestine perforation Small intestinal perforation Small intestinal ulcer perforation

The AEIs will be summarized similarly to TEAEs by dose level cohort.

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 FAS 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 SI units. When values are below the LOQ, they will be listed as such, and the closest imputed value will be used for the purpose of calculating summary statistics as specified in Section 3.7.

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

7.2.1. Summaries of Numeric Laboratory Results

Descriptive statistics will be provided by dose level cohort for each laboratory test specified in the study protocol as follows:

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

A baseline laboratory value will be defined as the last measurement obtained on or prior to the date/time of first dose of study drug. Change from baseline to a postbaseline visit will be defined as the visit value minus the baseline value. The mean, median, Q1, Q3, minimum, and maximum values will be displayed to the reported number of digits; StD 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 3.8.3.

7.2.2. Graded Laboratory Values

The CTCAE, Version 4.03, will be used to assign toxicity grades (0 to 4) to laboratory results for analysis. Grade 0 includes all values that do not meet the criteria for an abnormality of at least Grade 1. For laboratory tests with criteria for both increased and decreased levels, analyses for each direction (ie, increased, decreased) will be presented separately. Only local labs will be collected for this study and will be graded based on central lab normal ranges with an in-house macro.

7.2.2.1. Treatment-Emergent Laboratory Abnormalities

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

7.2.2.2. Summaries of Laboratory Abnormalities

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

The following summaries (number and percentage of subjects) for treatment-emergent laboratory abnormalities will be provided by lab test and dose level cohort; subjects will be categorized according to the most severe postbaseline abnormality grade for a given lab test. For all summaries of laboratory abnormalities, the denominator is the number of subjects in the FAS.

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

7.2.3. Liver-related Laboratory Evaluations

7.2.3.1. Transaminase Elevation

Analyses of transaminase elevations will be based on laboratory values using the FAS. The number and percentage of subjects will be summarized by dose level cohort:

- with Grade 3 or 4 treatment-emergent alanine aminotransferase (ALT)/ aspartate aminotransferase (AST) elevation
- with Grade 3 or 4 treatment-emergent ALT/AST elevation that resolved to both ALT and AST of Grade 1 or less

7.2.3.2. Liver-Related Laboratory Evaluations

The number and percentage of subjects will be summarized for the following liver-related laboratory tests and categories:

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

The summary will include data from all postbaseline visits up to 30 days after the last dose of study drug. For individual laboratory tests, subjects will be counted once based on the most severe postbaseline values. For both the composite endpoint of AST or ALT and total bilirubin, subjects will be counted once when the criteria are met at the same postbaseline visit date. The denominator is the number of subjects in the FAS who have nonmissing postbaseline values of all relevant tests at the same postbaseline visit date.

In addition, a listing of subjects who met at least 1 of the above criteria will be provided.

7.2.4. Shifts Relative to the Baseline Value

Shift tables will be presented by showing change in severity grade from baseline to worst grade post baseline.

7.3. Body Weight and Vital Signs

Descriptive statistics will be provided by dose level cohort for body weight and vital signs as follows:

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

A baseline value will be defined as the last available value collected on or prior to the date of first dose of study drug. Change from baseline to a postbaseline visit will be defined as the postbaseline value minus the baseline value.

In the case of multiple values in an analysis window, data will be selected for analysis as described in Section 3.8.3. No formal statistical testing is planned.

A by-subject listing of vital signs will be provided by subject ID number and visit in chronological order.

7.4. Prior and Concomitant Medications

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

7.4.1. Prior Medications

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

A summary of prior medications will not be provided.

7.4.2. Concomitant Medications

Concomitant medications are defined as medications taken while a subject took study drug. Use of concomitant medications will be summarized by preferred name using the number and percentage of subjects for each dose level. A subject reporting the same medication more than once will be counted only once when calculating the number and percentage of subjects who received that medication. The summary will be ordered by preferred term in descending overall frequency. For drugs with the same frequency, sorting will be done alphabetically.

For the purposes of analysis, any medications with a start date prior to or on the first dosing date of study drug and continued to be taken after the first dosing date, or started after the first dosing date but prior to or on the last dosing date of study drug will be considered concomitant medications. Medications started and stopped on the same day as the first dosing date or the last dosing date of study drug will also be considered concomitant. Medications with a stop date prior to the date of first dosing date of study drug or a start date after the last dosing date of study drug will be excluded from the concomitant medication summary. If a partial stop date is entered, any medication with the month and year (if day is missing) or year (if day and month are missing) prior to the date of first study drug administration will be excluded from the concomitant medication summary. If a partial start date is entered, any medication with the month and year (if day is missing) or year (if day and month are missing) after the study drug stop date will be excluded from the concomitant medication summary. Medications with completely missing start and stop dates will be considered as a concomitant medication.

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. Other Safety Measures

A data listing will be provided for subjects who became pregnant during the study.

Data listings will also be provided for surgeries and procedures, bone marrow assessment, performance status, and transfusion.

7.6. Changes From Protocol-Specified Safety Analyses

Due to the early study termination, only safety-related endpoints will be listed for the subjects enrolled in the study.

8. PHARMACOKINETIC ANALYSES

Individual subject concentration data for idelalisib, its metabolite GS-563117, and ruxolitinib will be listed and summarized using descriptive statistics by dose level cohort and visit. Summary statistics (n, mean, StD, coefficient of variation [%CV], median, min, max, Q1, and Q3) will be presented for individual subject concentration data by time point.

9. SOFTWARE

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

10. SAP REVISION

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

11. APPENDICES

Appendix 1. Schedule of Assessments

Weeks 1 to 4

Period	Screening	Treatment																								
Week		1												2											3	4
Study Day	-28 to -1	1	4											10											15	22
Hours relative to dosing			Pre dose	0	0.5	1	1.5	2	3	4	6	8	12	Pre dose	0	0.5	1	1.5	2	3	4	6	8	12		
Informed consent	X																									
MPN-SAF[a]		X												X											X	X
Medical & medication history[b]	X																									
Vital signs[c]	X	X	X											X											X	X
Physical exam[d]	X	X												X											X	X
ECOG	X	X												X											X	X
DIPSS[e]	X																									
12-lead ECG	X																									
Hematology[f]	X	X												X											X	X
Chemistry[g]	X	X												X											X	X
Urinalysis	X																									
ESR		X																								
Coagulation	X																									
Pregnancy test[h]	X	X																								
HIV screen	X																									
Pneumocystis jiroveci pneumonia (PJP) Prophylaxis [s]			X											X											X	X

Period	Screening	Treatment																								
Week		1												2											3	4
Study Day	-28 to -1	1	4											10											15	22
Hours relative to dosing			Pre dose	0	0.5	1	1.5	2	3	4	6	8	12	Pre dose	0	0.5	1	1.5	2	3	4	6	8	12		
CMV Testing[r]	X																									X
Immune Monitoring	X																									X
Hepatitis serology	X																									
Ruxolitinib PK[i]		X	X		X	X	X	X	X	X	X	X	X													
Idelalisib & Ruxolitinib PK[j]														X		X	X	X	X	X	X	X	X	X	X	
CCI																										
Bone marrow biopsy and aspirate[l]	X																									
Ruxolitinib dosing[m]		X		X									X		X								X	X	X	X
Idelalisib dosing[n]															X								X	X	X	X
Idelalisib dispensing, accountability[o]			X											X										X	X	X
AE, Conmeds[p]	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
MRI[q]	X																									

a The MPN-SAF will be completed weekly from Week 1 to 24 then monthly after Week 24 and at EOS. When visits are scheduled, it should be completed at the clinic. Subjects will receive a copy of the questionnaire to complete at home between clinic visits beginning Week 4.
b The medical and medication history will include the *JAK2*V617F mutation status if known, ruxolitinib dose and transfusion history within 3 months of screening.
c Vital signs include blood pressure, heart rate, respiratory rate, and oral temperature.
d Body weight, palpation of the spleen and liver will be performed at each PE. Height will be performed at screening only.
e DIPSS Plus should be completed for subjects who have cytogenetics information.

f Hematology: CBC with differential, reticulocyte count. ANC monitored at least every two weeks for the first 24 weeks of idelalisib treatment.
g Chemistry: Comprehensive metabolic panel with ALT, AST, GGT, iron, LDH, magnesium, phosphorus total bilirubin, direct bilirubin, uric acid.
h For females of childbearing potential only. Serum pregnancy test will be performed during screening only. A urine pregnancy test will be obtained throughout the rest of the study.
i The ruxolitinib Day 1 PK sample will be drawn predose. The 12 hour postdose PK time point on Day 4 will be performed prior to the second ruxolitinib dosing.
j Blood samples will be collected for ruxolitinib, idelalisib and/or metabolite PK beginning Day 10. The 12 hour post dose PK time point on Day 10 will be performed prior to idelalisib and ruxolitinib dosing. Beginning Day 15 PK samples will be collected predose and 1.5 hours postdose.
[redacted]
l Bone marrow biopsy and aspirate will be collected at Screening if one has not been done in the past 3 months or results are not available, Days 78, 162 and every 24 weeks during the extension period. It will also be collected at EOS, if one has not been done in the past 24 weeks. Bone marrow studies include cytogenetics, core biopsy, trichrome stain for reticulin, and iron stain.
m Ruxolitinib dosing will be in clinic when visits are scheduled.
n Idelalisib dosing will be in the clinic when visits are scheduled.
o Idelalisib will be dispensed in clinic on Day 4 for the subject to self-administer beginning Day 5. Idelalisib accountability should be done at every clinic visit.
p Adverse events and concomitant medications will be assessed and documented throughout the study. For assessment of Diarrhea/Colitis see Section 6.2.17 of the protocol.
q Three dimensional MRI (or CT, if MRI not feasible) for the liver and spleen size by volumetric imaging. An MRI should be done at the EOS visit only if it has not been done within 12 weeks of the visit.
r CMV testing will be performed every 4 weeks starting at Screening and end at EOS.

Weeks 6 to 24

Period	Treatment										Extension period[o]			EOS[q]	Follow Up[r]
Week	6	8	10	12	14	16	18	20	22	24	Q4W	Q12W[p]	Q24W[p]		
Study Day	36	50	64	78	92	106	120	134	148	162					
Visit Window (Days)	±3	±3	±3	±3	±3	± 3	±3	±3	±3	±3	±3	±3	±3		30 ± 7 days after EOS
MPN-SAF[a]	X	X	X	X	X	X	X	X	X	X	X			X	
Vital signs[b]	X	X	X	X	X	X	X	X	X	X	X			X	X
Physical exam[c]	X	X	X	X		X		X		X	X			X	X
ECOG	X	X	X	X		X		X		X	X			X	X
Hematology[d]	X	X	X	X	X	X	X	X	X	X	X			X	X
Chemistry[e]	X	X	X	X	X	X	X	X	X	X	X			X	X
CMV Testing[s]		X		X		X		X		X	X	X	X	X	
Immune Monitoring				X						X		X	X	X	
Pregnancy test[f]	X			X		X		X		X	X			X	X
Idelalisib & Ruxolitinib PK[g]	X			X						X					
CCI															
Bone marrow biopsy and aspirate[i]				X						X			X	X	
Ruxolitinib dosing[j]	X	X	X	X	X	X	X	X	X	X	X				
Idelalisib dosing[k]	X	X	X	X	X	X	X	X	X	X	X				
Idelalisib dispensing, accountability[l]	X	X	X	X	X	X	X	X	X	X	X			X	
AE, Conmeds[m]	X	X	X	X	X	X	X	X	X	X	X			X	X
MRI[n]				X						X		X		X	

a The MPN-SAF will be completed weekly from Week 1 to 24 then monthly after Week 24 and at EOS. When visits are scheduled, it should be completed at the clinic. Subjects will receive a copy of the questionnaire to complete at home between clinic visits beginning Week 4.
b Vital signs include blood pressure, heart rate, respiratory rate and oral temperature.
c Body weight, palpation of the spleen and liver will be performed at each PE. Height will be performed at screening only. Physical exams will be scheduled every 4 weeks during the extension period except after a subject has been on study for 1 year, when it will be scheduled every 12 weeks.
d Hematology: CBC with differential, reticulocyte count. ANC monitored at least every two weeks for the first 24 weeks of idelalisib treatment.

e Chemistry: Comprehensive metabolic panel with ALT, AST, GGT, iron, LDH, magnesium, total bilirubin, phosphorus, uric acid.
f For females of childbearing potential only. Serum pregnancy test will be performed during screening only. A urine pregnancy test will be obtained throughout the rest of the study.
g Blood samples will be collected for ruxolitinib, idelalisib and/or metabolite PK beginning Day 10. Beginning Day 15 PK samples will be collected predose and 1.5 hours postdose.
[redacted]
i Bone marrow biopsy and aspirate will be obtained at screening if one has not been done in the past 3 months or results are not available, Days 78, 162 and every 24 weeks during the extension period. It will also be obtained at EOS if one has not been done in the past 24 weeks. Bone marrow studies include cytogenetics, core biopsy, trichrome stain for reticulin, and iron stain.
j Ruxolitinib dosing will be in clinic when visits are scheduled.
k Idelalisib dosing will be in the clinic when visits are scheduled.
l Idelalisib will be dispensed in clinic on Day 4 for the subject to self-administer beginning Day 5. Idelalisib accountability should be done at every clinic visit.
m Adverse events and concomitant medications will be assessed and documented throughout the study. For assessment of Diarrhea/Colitis please see Section 6.2.17 of the protocol.
n Three dimensional MRI (or CT, if MRI not feasible) for the liver and spleen size by volumetric imaging. An MRI should be done at the EOS visit only if it has not been done within 12 weeks of the visit.
o If subjects are deriving clinical benefit (as determined by the investigator) and complete Week 24, subjects can enter extension period until they demonstrate progressive disease and/or have unacceptable toxicity, as defined by the protocol. Physical exams will be scheduled every 4 weeks during the extension period except after a subject has been on study for 1 year, when it will be scheduled every 12 weeks.
p Q12W and Q24W assessments will overlap with Q4W assessments and will be scheduled at the same visit.
q If the EOS visit coincides with Week 24 (Day 162), the predose blood sample for PK must be collected.
r The safety follow up visit is within 30 days of EOS.
s CMV testing will be performed every 4 weeks starting at Screening and end at EOS.

Appendix 2. Rash Medical Search Term

MedDRA Term Name	MedDRA Code
Acute generalised exanthematous pustulosis	10048799
Angina bullosa haemorrhagica	10064223
Autoimmune dermatitis	10075689
Blister	10005191
Blister rupture	10073385
Butterfly rash	10067982
Cervical bulla	10050019
Dermatitis exfoliative	10012455
Dermatitis exfoliative generalised	10012456
Dermatosis	10048768
Drug eruption	10013687
Drug reaction with eosinophilia and systemic symptoms	10073508
Eosinophilic pustular folliculitis	10052834
Epidermolysis	10053177
Epidermolysis bullosa	10014989
Eruptive pseudoangiomatosis	10068095
Erythema multiforme	10015218
Erythema nodosum	10015226
Erythrosis	10056474
Exfoliative rash	10064579
Fixed eruption	10016741
Flagellate dermatitis	10075467
Interstitial granulomatous dermatitis	10067972
Lichenoid keratosis	10064000
Macule	10025421
Mucocutaneous rash	10056671
Mucocutaneous ulceration	10028084
Mucosa vesicle	10028103
Necrolytic migratory erythema	10060821
Neurodermatitis	10029263
Oculomucocutaneous syndrome	10030081
Oral mucosal blistering	10030995

MedDRA Term Name	MedDRA Code
Oropharyngeal blistering	10067950
Palmar-plantar erythrodysaesthesia syndrome	10033553
Palpable purpura	10056872
Papule	10033733
Paraneoplastic rash	10074687
Pemphigoid	10034277
Pemphigus	10034280
Penile blister	10052898
Prurigo	10037083
Rash	10037844
Rash erythematous	10037855
Rash follicular	10037857
Rash generalised	10037858
Rash macular	10037867
Rash maculo-papular	10037868
Rash maculovesicular	10050004
Rash morbilliform	10037870
Rash papular	10037876
Rash papulosquamous	10037879
Rash pruritic	10037884
Rash pustular	10037888
Rash rubelliform	10057984
Rash scarlatiniform	10037890
Rash vesicular	10037898
Seborrhoeic dermatitis	10039793
Skin disorder	10040831
Skin plaque	10067723
Skin reaction	10040914
Skin toxicity	10059516
Stevens-Johnson syndrome	10042033
Symmetrical drug-related intertriginous and flexural exanthema	10078325
Toxic epidermal necrolysis	10044223

MedDRA Term Name	MedDRA Code
Toxic erythema of chemotherapy	10074982
Toxic skin eruption	10057970
Umbilical erythema	10055029
Urticarial vasculitis	10048820
Vaginal exfoliation	10064483
Vasculitic rash	10047111
Viral rash	10047476
Vulvovaginal rash	10071588