Janssen Pharmaceutical K.K.*

Statistical Analysis Plan

A Phase 3 Study of the Bruton's Tyrosine Kinase (BTK) Inhibitor Ibrutinib in Subjects with Steroid Dependent/Refractory Chronic Graft Versus Host Disease (cGVHD)

Protocol 54179060GVH3001; Phase 3

JNJ-54179060 (Ibrutinib)

* This study is being conducted by Janssen Pharmaceutical K.K. in Japan. The term "sponsor" is used throughout the protocol to represent Janssen Pharmaceutical K.K.

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Compliance: The study described in this report was performed according to the principles of Good Clinical Practice (GCP).

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AMENDMENT HISTORY

SAP Version	Issue Date
Original SAP	15 March 2018
Amendment 1	25 February 2020
Amendment 2	13 January 2022

Amendment 2 (13 January 2022)

The overall reason for the amendment: to update and clarify the details.

Applicable Section(s)	Description of Change (s)
Section 4.4	Added 'COVID-19 related protocol deviations will be provided in a separate listing'.
Section 6.1.1	Updated the definition of Cardiac arrhythmia as 'Cardiac arrhythmia will be determined based on Cardiac arrhythmias (SMQ, broad and narrow) ~~and Ventricular tachyarrhythmias (SMQ, narrow)~~.'.
Section 6.1.1	Updated the definition of CNS hemorrhage to remove manual medical review.
Section 6.1.1	Added ischemic stroke and cardiac failure for AE of special interest.

Amendment 1 (25 February 2020)

The overall reason for the amendment: to update and clarify the details.

Applicable Section(s)	Description of Change (s)
Section 2.9	Added 'Assigned daily dose is 420 mg, unless dose is modified due to the use of CYP3A inhibitor or study drug discontinuation'.
Section 4.1	Added 'Daily Steroid Dose per Weight at baseline (mg/kg/day)' to baseline disease characteristics information.
Section 4.3	Added 'Time on study'.
Section 4.5	Added 'Medical history collected at baseline or screening visit will be summarized by system-organ class and preferred term for all treated analysis set'.
Section 4.6	Change from 'the day of ICF (partial or complete) of study agent' to 'the first dose of the study agent'. Added 'Concomitant use of additional immunosuppressants will be summarized and listed'.
Section 6.1	Updated planned tables.
Section 6.1.1	Added AEs of special interest, 'Other Malignancies', 'Hypersensitivity' and 'CNS Hemorrhage'.
Section 6.2	Added subjects who died during the study.
Section 6.5	Added subjects who died in the study.
Section 7.1	Added Subgroup analysis by concomitant CYP3A inhibitors.

ABBREVIATIONS

AE	adverse event
ALT/SGPT	alanine aminotransferase
AST/SGOT	aspartate aminotransferase
BTK	Bruton's Tyrosine Kinase
BUN	blood urea nitrogen
cGVHD	Chronic Graft Versus Host Disease
CI	confidence interval
Cmax	maximum concentration
CR	complete response
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
DOR	duration of response
ECG	electrocardiogram
eCRF	electronic case report form
FAS	full analysis set
FEV1	forced expiratory volume in 1 second
FFS	failure free survival
LDH	lactic acid dehydrogenase
ILD	interstitial lung disease
MedDRA	Medical Dictionary for Regulatory Activities
OS	Overall survival
PD	pharmacodynamic
PI	principal investigator
PK	pharmacokinetic(s)
PR	partial response
PT	preferred term
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SOC	system organ class
SMQs	standardised MedDRA queries
TEAE	treatment-emergent adverse event
Tmax	time to maximum concentration
WBC	white blood cell
WHO	World Health Organization
WHO-DD	World Health Organization Drug Dictionary

1. INTRODUCTION

This Statistical Analysis Plan (SAP) covers Primary Analysis and Final Analysis. It contains definitions of analysis sets, derived variables and statistical methods for analyses of efficacy, safety, pharmacokinetic (PK) and pharmacodynamics (PD) data of study 54179060GVH3001.

1.1. Trial Objectives

Primary objective:

Evaluate efficacy of ibrutinib in Japanese subjects with steroid dependent/refractory cGVHD by measuring overall cGVHD response (Complete Response [CR] and partial response [PR] defined by NIH Consensus Development Project Criteria [2014]).

Secondary objectives:

- Evaluate efficacy of ibrutinib in Japanese subjects with steroid dependent/refractory cGVHD by measuring:
  - Rate of sustained response for at least 20 weeks
  - Duration of response (DOR)
  - cGVHD response rate at each timepoint of efficacy evaluation
  - Corticosteroid requirement changes over time
  - Change in symptom burden measured by the Lee cGVHD Symptom Scale
- Evaluate the safety of ibrutinib in Japanese subjects with steroid dependent/refractory cGVHD
- Evaluate the pharmacokinetics (PK) of ibrutinib in Japanese subjects with cGVHD

Exploratory objectives:

- Evaluate efficacy of ibrutinib by measuring:
  - Failure free survival (FFS)
  - Overall survival (OS)
  - Number and proportion of subjects with all immunosuppressants withdrawn
- Evaluate the BTK and ITK binding site occupancy as a pharmacodynamic (PD) parameters

1.2. Trial Design

This is an open-label, single arm, multicenter Phase 3 study to evaluate the efficacy, safety, and PK of single-agent ibrutinib 420 mg in Japanese subjects 12 years of age or older with steroid dependent/refractory cGVHD. Approximately 20 subjects will be enrolled to have 17 response evaluable subjects. At least 1 adolescent subject (12-17 years of age) will be enrolled in this study.

Subject participation will include a Screening Phase, a Treatment Phase, and a Posttreatment Follow-up Phase. The Screening Phase assessments will be performed within 42 days prior to study treatment initiation. The Treatment Phase will extend from first dose of study treatment until treatment discontinuation. During the Treatment Phase, efficacy and safety evaluations, sampling of PK and PD will be performed. The Posttreatment Follow-up Phase will begin once a subject discontinues ibrutinib treatment. Subjects who discontinue treatment for reasons other than cGVHD progression will complete an End-of-treatment Visit and will be followed for the cGVHD evaluations until cGVHD progression, death, loss to follow-up, consent withdrawal, or study end, whichever occurs first. Subjects who discontinue due to cGVHD progression will complete an End-of-treatment Visit and be followed for survival status and the use of subsequent cGVHD treatment.

1.3. Statistical Hypotheses for Trial Objectives

The primary hypothesis of this study is that ibrutinib is an effective agent as measured by an overall cGVHD response rate (the lower bound of 95% confidence interval is greater than 25%) in Japanese subjects with steroid dependent/refractory cGVHD.

1.4. Sample Size Justification

With a sample size of 17 subjects and assuming an expected overall cGVHD response rate of approximately 60%, it is expected to have at least 80% power to show the efficacious treatment effect (the lower bound of 95% confidence interval of the response rate >25%). At least 1 adolescent subject (12-17 years of age) will be enrolled in this study.

1.5. Randomization and Blinding

This is an open label study, so no randomization and blinding will occur.

2. GENERAL ANALYSIS DEFINITIONS

2.1. Visit Windows

For visitwise analysis, CRF-recorded visits will be followed.

The visit windows are described in “Time and Events Schedule” of the protocol. For visitwise evaluation of pharmacokinetics and pharmacodynamics data of ibrutinib, allowance described in “Time and Events Schedule” will be applied to actual time of CRF-recorded time point.

2.2. Pooling Algorithm for Analysis Centers

No pooling of analysis centers will be performed in this study.

2.3. Analysis Sets

2.3.1. All Treated Analysis Set

The all treated analysis set includes all enrolled subjects who received at least 1 dose of study drug.

2.3.2. Response Evaluable Analysis Set

All enrolled subjects who will receive at least 1 dose of study drug and who have at least 1 adequate postbaseline efficacy assessment.

2.3.3. Safety Analysis Set

The safety analysis set includes all enrolled subjects who received at least 1 dose of study drug. Safety analysis set is identical to all treated analysis set.

2.3.4. Pharmacokinetics Evaluable Analysis Set

The PK evaluable analysis set is defined as all enrolled subjects who have received at least one dose of study drug and have at least 1 postdose PK sample obtained.

2.3.5. Pharmacodynamics Evaluable Analysis Set

The PD evaluable analysis set is defined as all enrolled subjects who have received at least one dose of study drug and have at least 1 BTK and ITK binding site occupancy data.

2.4. Study Day and Relative Day

Study Day 1 or Day 1 refers to the start of the first study drug administration. All efficacy and safety assessments at all visits will be assigned a day relative to this date.

Study day or relative day for a visit is defined as:

- Visit date - (date of Study Day 1) +1, if visit date is ≥date of Study Day 1
- Visit date - Date of Day 1, if visit date <date of Study Day 1

There is no 'Day 0'.

2.5. Baseline

Baseline is defined as the last observation on or prior to the first study drug administration.

2.6. Treatment Duration

Treatment duration will be calculated from the date of the first dose of study drug to the date of the last dose of study drug, as follows:

Treatment Duration = date of last dose of study drug – date of first dose of study drug +1 day.

2.7. Time on Study

Time on Study will be calculated from the first study drug administration date to the study exit date or the last known alive date if the subjects are still in the study, as follows:

Time on Study = study exit date/last known alive date – first study drug administration date +1 day.

2.8. Dose Intensity

The dose intensity (mg/day) of study agent is calculated as (sum of total daily dose during the treatment phase)/study agent duration.

2.9. Relative Dose Intensity

Relative dose intensity (%) is defined as the percentage of total cumulative dose administered (mg) versus the total expected dose (mg). Total cumulative dose administered is the sum of daily dose taken over the whole study course; and total expected dose (mg) is the product of the duration of the treatment (day) and the assigned daily dose. Assigned daily dose is 420 mg, unless dose is modified due to the use of CYP3A inhibitor or study drug discontinuation. Relative dose intensity is calculated by total cumulative dose administered / total expected dose ×100%.

2.10. Imputation Rules for Missing Dates

In general, imputation of missing dates will be made for AE onset date, AE resolution date, date of death, start and end dates of prior and concomitant and subsequent therapies, transplantation date, and date of initial diagnosis according to the following rules.

- If the date is completely missing, no imputation will be made.
- If the year is missing, then no imputation will be made.
- If only the year is present but the month and day are missing, then June 30th will be used.
- If only the day is missing but the year and month are available, then the 15th of the month will be used.

In addition, for date of initial diagnosis, the imputed date will be adjusted sequentially using the following steps:

- If only the day is missing;
  - if month and year of start of 1st line of prior therapy are the same year and month of diagnosis, and day of start date of 1st line of prior therapy is available, then the day of start date of 1st line of prior therapy will be used.
  - otherwise, the 15th of the month will be used.
- If both month and day are missing;
  - if year of diagnosis is the same as year of start of 1st line of prior therapy, and month info is available for start date of the 1st line of prior therapy, the month of start date of 1st line of prior therapy will be used.
    - if day of start date of 1st line of prior therapy is available, then the day of start date of 1st line of prior therapy will be used.
    - otherwise, the 15th of the month will be used.
  - otherwise, June 30th will be used.

- If the imputed date for initial diagnosis is on or after the first dose date, then first dose date -1 day will be used.

In addition, for date of prior and subsequent therapies, the imputed date will be adjusted sequentially using the following steps:

- If such imputed date for prior therapies is on or after the first dose date, then first dose date -1 day will be used.
- If such imputed date for subsequent therapies is before date of last dose, then date of last dose +1 day will be used.
- If prior or subsequent therapy start date is not missing and is after the imputed end date, then the start date will be used as the end date.
- If prior or subsequent therapy end date is not missing and is before the imputed start date, then the end date will be used as the start date.

In addition, for AE date, the above imputations will be modified by the following rules:

- The imputed start date of adverse event will be adjusted sequentially using the following steps:
  - If the imputed date is in the same year and month but before the first dose date, then the first dose date will be used, or if it is in the same year and month but after the last dose date +30 days, then the last dose date +30 days will be used.
  - If end date of adverse event is not missing and the imputed start date of adverse event is after the end date of adverse event, then the end date of adverse event will be used.
  - If the imputed start date of adverse event is after date of death, then the date of death will be used.
  - If the imputed start date of adverse event is in the same month and year but after the start date of 1st subsequent therapy, then the start date of 1st subsequent therapy will be used.
- The imputed end date of adverse event will be adjusted sequentially using the following steps:
  - If the imputed end date of adverse event is after the death date, then the death date will be used.
  - If the imputed end date of adverse event is before the start date of adverse event, then the start date of adverse event will be used.

In addition, for start and end dates of concomitant therapy, the adverse event imputation rule will be used for concomitant therapy.

3. INTERIM ANALYSIS AND DATA MONITORING COMMITTEE REVIEW

No interim analysis will be conducted in this study.

4. SUBJECT INFORMATION

4.1. Demographics and Baseline Characteristics

List of the demographic and baseline characteristics, presented in Table 1, will be summarized for the all treated analysis set.

Table 1: Demographic and Baseline Characteristics Variables

Continuous Variables:	**Summary Type**
Age (years)	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum].
Weight (kg)	
Height (cm)	
Baseline hemoglobin (g/L)	
Baseline platelets (10^9/L)	
Baseline Absolute neutrophil count (10^9/L)	
Baseline Bilirubin	
Categorical Variables	
Sex (male, female, unknown,undifferentiated)	Frequency distribution with the number and percentage of subjects in each category.
Race (Asian)	
Ethnicity (Hispanic or Latino, not Hispanic or Latino)	

Following baseline disease characteristics information will be summarized for all treated subjects:

- cGVHD Disease State (Steroid Dependent, Steroid Refractory)
- Overall Severity of cGVHD (1, 2, 3, NA)
- Months from Last Transplantation to Enrollment, which is defined as the time period between the last transplantation and enrollment
- Months from Initial cGVHD Diagnosis Date, which is defined as the time period between the initial cGVHD diagnosis and enrollment
- Months from Transplantation to initial cGVHD diagnosis date
- Karnofsky performance status score at baseline
- Lansky performance status score at baseline
- Number of prior cGVHD treatment regimens
- Organs involved in cGVHD
- Daily Steroid Dose per Weight at baseline (mg/kg/day)

4.2. Disposition Information

The number of subjects in the following disposition categories will be summarized throughout the study using all treated analysis set:

- Subjects screening
- Subjects receiving study agent
- Subjects ongoing treatment

- Subjects completing the study
- Subjects who discontinued study agent
- Reasons for discontinuation of study agent
- Subjects who terminated study prematurely
- Reasons for termination of study
- Analysis Sets

Listings of subjects will be provided for the following categories:

- Subjects who discontinued study agent
- Subjects who terminated study prematurely

4.3. Extent of Exposure

Descriptive statistics (N, mean, SD, median, and range (minimum, maximum)) will be presented for the following parameters:

- Treatment duration
- Cumulative total dose
- Dose intensity
- Relative dose intensity
- Time on Study

Dose withholding (any dose skip with 7 days or more) and dose reduction will be summarized for the number of subjects with any dose withholding (at least one reported dose withholding), any dose reduction (at least one reported dose reduction), and any dose modification (at least one dose withholding or dose reduction), as well as the frequency and reason of dose withholding and dose reduction.

4.4. Protocol Deviations

In general, protocol violations/deviations will be reviewed by the study team during the study, and important protocol deviations will be determined based on the review. The information of important protocol deviations will be generated based on the review outcome for all subjects. Important protocol deviations will be summarized by center. A corresponding listing is also generated. COVID-19 related protocol deviations will be provided in a separate listing.

4.5. Medical History

Medical history collected at baseline or screening visit will be summarized by system-organ class and preferred term for all treated analysis set. Transplant history and underlying disease will be summarized and listed.

4.6. Prior and Concomitant Medications

Concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO-DD). Prior medications are defined as any therapy used before the first dose of the study agent. Concomitant medications are defined as any therapy used on or after the same day as the first dose of study agent, including those that started before and continue on after the first dose of study agent.

Summaries of concomitant medications will be presented by therapeutic class and preferred term. In addition, summary of usage of CYP3A inhibitors as well CYP3A inducers will be provided separately. A list of common CYP3A inhibitors and inducers is provided in Attachment 1. The summary of usage of anticoagulants and antiplatelets will also be provided.

Prior and subsequent cGVHD therapies after the start of study drug will be summarized and listed separately. Concomitant use of additional immunosuppressants will be summarized and listed.

5. EFFICACY

5.1. Analysis Specifications

5.1.1. Level of Significance

All tests will be 1-sided. The primary efficacy endpoint will be tested at the overall significance level of 0.025. For result presentation purpose, a 2-sided 95% confidence interval will be used.

5.1.2. Data Handling Rules

Unless specified otherwise, missing values will not be imputed and partial dates are described in Section 2.10.

5.2. Primary Efficacy Endpoint(s)

The overall response rate (ie, the proportion of responders [CR or PR]).

5.2.1. Definition

Response will be defined by the NIH Consensus Development Project Criteria (2014) and must occur:

- In the absence of new therapy for cGVHD
- In the absence of progression of the underlying disease that was the indication for transplant (or posttransplant lymphoproliferative disease [PTLD]), or death.

5.2.2. Analysis Methods

The all treated analysis set will be used for primary endpoint. The response evaluable analysis set will be used for sensitivity analysis.

The primary analysis for primary endpoint will be conducted at the time when the last subject has completed the efficacy assessment at Week 37 or has discontinued treatment before Week 37. Final analysis will be conducted at the study end.

The overall cGVHD response rate (CR + PR) and its 95% confidence interval will be calculated with the exact test for binomial distribution in the all treated population. The study is considered to be positive if the lower limit of the exact 2-sided 95% confidence interval based on binominal distribution exceeds the threshold value (0.25).

5.3. Major Secondary Endpoints

The secondary efficacy endpoints are:

- Rate of sustained response for at least 20 weeks
- Duration of response
- cGVHD response rate at each timepoint
- Corticosteroid requirement changes over time
- Change in symptom burden measured by the Lee cGVHD Symptom Scale

5.3.1. Definition

Sustained Response:

Sustained response is defined as NIH-defined response that sustain continuously for at least 20 weeks (140 days). Considering 7 days at maximum visit window allowed by protocol, the bound of sustained response is defined as 133 days. Intermittent SD assessment between response assessments is allowed.

Duration of Response:

Duration of Response (DOR) is defined as the interval between the date of initial documentation of a response (CR or PR), and the date of first documented evidence of progressive disease, death, or date of censoring if applicable, for responders only. DOR will be right censored based on Table 2 for all responders:

Table 2: Date of Event or Censoring for Duration of Response

Situation	Date of DOR Event or Censoring	Outcome
Death or disease progression occurred on or before the start date of subsequent cGVHD treatment documented at scheduled disease assessments or between two scheduled disease assessments.	Earliest date of adequate disease assessment documenting disease progression or date of death, whichever occurs first.	Event
New subsequent cGVHD treatment before disease progression	Date of last adequate disease assessment prior to or on start date of the new subsequent cGVHD treatment	Censored
Not known to have progressed or died at the data analysis cutoff date (this includes subjects who were known to have progressed or died after the data analysis cutoff date)	Date of last adequate disease assessment showing no evidence of disease progression.	Censored

For subjects who met more than one censoring condition, DOR will be censored according to the earliest censoring condition/date. For subjects who have incomplete date for initiation of subsequent cGVHD treatment, the partial date will be imputed as the earliest possible date that incorporates the available information from the partial date and does not contradict last dose date of study drug.

Corticosteroid Requirement Changes over Time:

Systemic corticosteroid therapy for cGVHD will be monitored throughout the study. The corticosteroid dose level will be measured by the daily dose amount versus the weight of subject (mg/kg/day). For the days without weight measurement, the last observed weight measurement will be used. Considering the frequency of corticosteroid use might not be once daily, we use weekly average daily dose instead of the actual daily dose. The average corticosteroid dose level in each week is calculated by

Sum of total corticosteroid dose used in this week / 7

If a subject terminated the study drug in the middle of the week, the average corticosteroid dose level in that week will be calculated by

Sum of total corticosteroid dose used in the week before the study drug termination / actual days in the week up to the last dose of study drug.

Change in Lee cGVHD Symptom Scale:

Subject-reported improvement in symptom burden will be evaluated. The symptom burden is measured according to the Lee cGVHD Symptom Scale.[1] There are 7 domains, and each has several items (refer to Table 3).

Table 3: Lee cGVHD Symptom Scale

Subscale	Related Items	Maximum No. of Missing Items to Get a Valid Score
Skin	1, 2, 3, 4, 5	2
Energy	14, 21, 22, 23, 24, 25, 26	3
Lung	12, 13, 15, 16, 27	2
Eye	6, 7, 8	1
Nutrition	11, 17, 18, 19, 20	2
Mouth	9, 10	1
Psychological	28, 29, 30	1

A score is calculated for each subscale by taking the mean of all items completed if more than 50% were answered and normalizing to a 0 to 100 scale. A total summary score is calculated as the average of these 7 subscales if at least 4 subscales have valid scores.

A change in ≥7 points on the Lee cGVHD Symptom Scale will be considered significant and relates to improvement in quality of life.[2]

5.3.2. Analysis Methods

The all treated population will be used for all secondary efficacy endpoints.

Rate of sustained response for at least 20 weeks will be calculated with the exact 2-sided 95% confidence interval based on binominal distribution.

The DOR for responders will be calculated by the Kaplan-Meier method descriptively. Median DOR and the corresponding 95% confidence interval will be provided if estimable with Kaplan-Meier plot.

The overall cGVHD response rate at each timepoint of efficacy evaluation will be summarized by descriptive statistics.

Corticosteroid requirement changes over time will be summarized by descriptive statistics by responder (CR or PR) and non-responder.

Change in symptom burden measured by the Lee cGVHD Symptom Scale will be summarized by descriptive statistics. A summary of total scores as well as each subscale scores for Lee cGVHD symptom scale will be performed throughout the study. A summary of the proportion of subjects who have decreases of at least 7 points in Lee cGVHD symptom scale during the study will be performed.

5.4. Other Efficacy Variable(s)

The exploratory efficacy endpoints are:

- Failure free survival (FFS)
- Overall survival (OS)
- Number and proportion of subjects with all immunosuppressants withdrawn
- Best organ response rate

5.4.1. Definition

Failure free survival (FFS):

Failure free survival (FFS) is defined as the duration from the date of initial dose to the date of relapse of malignancy, initiation of new immunosuppressive therapy for GVHD or death, whichever occurs first. FFS will be right censored based on Table 4.

Table 4: Date of Event or Censoring for Failure Free Survival

Situation	Date of FFS event or Censoring	Outcome
Death	Date of death	Event
New subsequent cGVHD treatment	Date of starting the new subsequent cGVHD treatment	Event
Relapse of malignancy	Start date of relapse of malignancy	Event
Not known to have event at the data analysis cutoff date (this includes subjects who were known to have event after the data analysis cutoff date)	Date of last known date (last visit) showing no evidence of event.	Censored

Overall survival (OS):

Overall survival (OS) is defined as the duration from the date of initial dose to the date of the subject's death. OS will be right censored if no death has occurred at the data analysis cutoff date.

Best organ response rate:

Best organ response rate is defined as the proportion of responders (CR or PR) in a specific organ or site. Skin, mouth, liver, upper CI, lower GI, esophagus, lung, eye, and joint/fascia are the organs or sites considered.

5.4.2. Analysis Methods

The Kaplan-Meier method will be used to descriptively summarize the FFS. Median FFS and the corresponding 95% confidence interval will be provided if estimable with Kaplan-Meier plot.

The OS will be evaluated in the same manner as FFS.

Number and proportion of subjects with all immunosuppressants withdrawn and organ response will be summarized by descriptive statistics.

6. SAFETY

Unless specified otherwise, all safety analyses will be based on Safety Analysis Set.

6.1. Adverse Events

The verbatim terms used in the CRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events will be graded by the investigator according the National Cancer Institute common terminology criteria for adverse events (CTCAE) Version 4.03. Any AE occurring at or after the initial administration of study agent through the day of last dose plus 30 days or initiation of subsequent cGVHD therapy is considered to be treatment-emergent. If the event date is recorded as partial or completely missing, then the event will be considered to be treatment-emergent unless it is known to be prior to the first administration of study agent based on partial onset date or resolution date. If the event is study drug-related regardless of the start date of the event, it is considered to be treatment-emergent. If an event that is present at baseline but worsens in severity or is subsequently considered drug-related by the investigator, then it is considered to be treatment-emergent. All reported treatment-emergent adverse events will be included in the analysis. For each adverse event, the number and percentage of subjects who experience at least 1 occurrence of the given event will be summarized.

Summary tables will be provided for:

- Overall summary of all treatment-emergent AEs(TEAEs)
- TEAEs by System Organ Class (SOC), preferred term (PT) and toxicity Grade 3 or higher
- TEAE with frequency of at least 10% by SOC, PT and toxicity Grade 3 or higher
- Drug-related TEAEs by SOC, PT and toxicity Grade 3 or higher

- Serious TEAEs by SOC, PT and toxicity Grade 3 or higher
- TEAEs leading to dose reduction by SOC, PT and toxicity Grade 3 or higher
- TEAEs leading to discontinuation of study drug by SOC, PT and toxicity Grade 3 or higher
- Fatal TE AEs by SOC and PT
- TEAEs by SOC, PT and toxicity by period

In addition to the summary tables, listings will be provided for subjects who:

- Had any AE
- Had SAEs
- Had TEAEs leading to dose modification
- Had TEAEs leading to discontinuation of study drug
- Had drug-related TEAEs
- Had Fatal TEAEs

Incidence of treatment-emergent adverse events of special interest will be summarized.

6.1.1. AEs of special interest (AESI)

Number and percent of subjects with following AESIs will be summarized by preferred terms.

Major hemorrhage

Major hemorrhage is defined as:

- Treatment-emergent hemorrhagic adverse event of Grade 3 or higher. All hemorrhagic events requiring a transfusion of red blood cells should be reported as Grade 3 or higher adverse events per NCI-CTCAE.
- Treatment-emergent SAE of Hemorrhagic event of any grade
- Treatment-emergent central nervous system hemorrhage/hematoma of any grade

Hemorrhagic event

Hemorrhagic events will be identified by hemorrhage Standardized MedDRA Query [SMQ] excluding laboratory terms.

Cardiac arrhythmia

Cardiac arrhythmia will be determined based on Cardiac arrhythmias (SMQ, broad and narrow).

Interstitial Lung Disease

Interstitial Lung Disease (ILD) will be determined based on Interstitial lung disease (SMQ, narrow). All treatment emergent ILD events will be summarized by preferred terms.

Severe Cutaneous Adverse Reaction

Severe Cutaneous Adverse Reaction (SCAR) will be determined based on Severe cutaneous adverse reactions (SMQ, narrow).

Hypertension

Hypertension will be determined based on Hypertension (SMQ, narrow).

Other Malignancies

Treatment-emergent Neoplasms benign, malignant and unspecified (incl cysts and polyps) of any grade (SOC). Relapse of underlying malignancy will not be considered as other malignancies.

Hypersensitivity

This definition will be specified in DPS, separatory.

CNS Hemorrhage

CNS hemorrhage is a subset of CNS related PTs in the hemorrhage SMQ.

Ischemic stroke

Ischemic stroke is determined based on Ischemic central nervous system vascular conditions (SMQ).

Cardiac failure

Cardiac failure is determined based on Cardiac failure SMQ (narrow).

6.2. Death

Subjects who died during the study will be listed.

6.3. Clinical Laboratory Tests

All clinical laboratory tests will be displayed for the subjects included in the safety analysis set. Laboratory data for hematology and serum chemistry tests will be reported in SI units. Applicable laboratory results will be graded according to NCI-CTCAE Version 4.03.

The following laboratory tests will be analyzed:

- Hematology: hemoglobin, platelet count, white blood cell (WBC) count, absolute neutrophil count (ANC), absolute lymphocyte count, and absolute eosinophil count
- Chemistry: sodium, potassium, glucose, total bilirubin, blood urea nitrogen (BUN), creatinine, total protein, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, lactic acid dehydrogenase (LDH), uric acid and albumin.
- Donor/host chimerism, serum immunoglobulin levels (IgG, IgM, IgA)

Descriptive statistics and change from baseline will be presented for all laboratory tests with continues values at scheduled time points.

Frequency tabulations of the changes from baseline results will be presented in pre versus postintervention cross-tabulations (with classes for Low, Normal, and High). Frequency tabulations of the abnormalities will be made. A listing of subjects with laboratory results will be provided. A listing of subjects with liver function abnormality will also be provided. Parameters with predefined NCI-CTCAE toxicity grades will be summarized. Change from baseline to the worst adverse event grade experienced by the subject during the study will be provided as shift tables.

6.4. Vital Signs and Physical Examination Findings

Continuous vital sign parameters including temperature, respiratory rate, weight, pulse and blood pressure (systolic and diastolic) will be summarized at each assessment time point. A listing will also be provided.

6.5. Death

Subjects who died in the study will be listed.

6.6. Other Safety Parameters

Descriptive summary will be provided for following parameters:

- Karnofsky/Lansky Performance Scale
- Forced expiratory volume in 1 second (FEV1).

Corresponding listings will also be provided.

7. PHARMACOKINETICS/PHARMACODYNAMICS

7.1. Pharmacokinetics

Pharmacokinetic evaluable analysis set will be used for PK analyses. The individual plasma concentration data of ibrutinib and PCI-45227 will be listed and graphically displayed (normal scale and semilog scale). Concentrations below the lowest quantifiable concentration or missing data will be labeled as such in the concentration data presentation. The data will be summarized at each timepoint using descriptive statistics (mean, standard deviation [SD], coefficient of variation, median, minimum and maximum) and mean (±SD) concentration-time profile will be graphically displayed (normal scale and semilog scale). Concentration data below the lowest quantifiable concentration will be treated as zero in the summary statistics. Subgroup analysis by concomitant CYP3A inhibitors will be performed. Additional analyses may be performed as deemed necessary.

For concentration summary, applying the following rules.

- When more than half (>50%) of concentration data are BQL at each scheduled time point, mean and median will be reported as ‘BQL’; SD and %CV are reported as ‘NC’; maximum and minimum will be reported as observed (including BQL).

- When number of concentration data are equal to or less than 2, SD, %CV, median, minimum and maximum will be shown as 'NC' regardless of the proportion of BQL.

The individual PK parameters (C_{max}, t_{max}, $t_{1/2}$, t_{last}, CL/F, Vd_z/F, AUC_{last}, AUC_{24}, AUC_∞ and λ_z) of ibrutinib and PCI-45227 will be calculated using noncompartmental analysis based on actual sampling times. Accumulation ratios based on C_{max} and AUC_{24} for Week 2 is derived for both ibrutinib and PCI-45227. Metabolite-to-parent ratio (MPR) based on C_{max}, AUC_{last}, AUC_{24} and AUC_∞ will be generated. Dose-normalized C_{max}, AUC_{last}, and AUC_{24} will be calculated to a 420 mg ibrutinib dose. Individual values (C_{max}, t_{max}, $t_{1/2}$, t_{last}, CL/F, Vd_z/F, AUC_{last}, AUC_{24}, AUC_∞, λ_z, dose-normalized C_{max}, AUC_{last}, and AUC_{24}, accumulation ratios based on C_{max}, accumulation ratio based on AUC_{24}, MPR based on C_{max}, MPR based on AUC_{last}, MPR based on AUC_{24} and MPR based on AUC_∞) will be listed and summarized for ibrutinib and PCI-45227 using descriptive statistics (mean, SD, coefficient of variation [CV], geometric mean, median, minimum and maximum [SD, CV, geometric mean are not needed for t_{max} and t_{last}]).

Subgroup analysis by ibrutinib dose and concomitant CYP3A inhibitors will be performed on the individual PK parameters of ibrutinib and PCI-45227 (C_{max}, t_{max}, $t_{1/2}$, t_{last}, AUC_{last}, AUC_{24}, AUC_∞ and λ_z). Only strong/moderate CYP3A inhibitors taken on the PK assessment days (Week 1, Day 1 and Week 2, Day 1) will be considered. The subgroups will be defined based on the name of the inhibitors (eg, fluconazole [ibrutinib dose: 420 mg]). Summary tables will be provided to present the summary statistics derived for each subgroup. In addition, individual and mean values of selected PK parameters (eg, C_{max}, AUC_{last}) will be graphically presented to visually compare the values between each subgroup. The graphical presentation will be performed for dose-normalized PK parameters (eg, dose-normalized C_{max}, AUC_{last}) regardless of ibrutinib dose.

Additional analyses may be performed as deemed necessary.

For PK parameter summary, applying the following rules.

- In the case following criteria are not met, $t_{1/2}$, AUC_∞, CL/F, Vd_z/F, λ_z, and MPR based on AUC_∞ will be reported with annotation as such and excluded from the descriptive statistics.
  - At least 3 data points are used in calculation for λ_z;
  - r^2_{adj} for the regression of $\lambda_z \geq 0.90$;
  - $\%AUC_{\infty,ex}$ is $\leq 20\%$.

Data or subjects will be excluded from the analysis if the data do not allow for accurate assessment of the PK. All subjects and samples excluded from the analysis will be clearly documented in the study report.

7.2. Pharmacodynamics

Pharmacodynamic evaluable analysis set will be used for PD analyses. The BTK and ITK binding site occupancy will be tabulated and summarized at each timepoint using descriptive statistics (mean, SD, coefficient of variation, median, minimum and maximum). Box plots of individual data at each time point will be presented in one panel. Additional analyses (eg,

subgroup analyses by ibrutinib dose or concomitant CYP3A inhibitors) may be performed as deemed necessary.

REFERENCES

1. Lee SJ, Cook EF, Soiffer R, Antin JH. Development and validation of a scale to measure symptoms of chronic graft-versus-host disease. Biologyu of Blood and Marrow Transplantation 2002;8:444-452.
2. Lee SJ, Kim HT, Ho VT, et al. Quality of life associated with acute and chronic graft-versus-host disease. Bone Marrow Transplant 2006;38:305-10.

ATTACHMENTS

ATTACHMENT 1: PLANNED LISTINGS

The details will be specified in the Data Presentation Specifications.

Output Title	Analysis Set
Subject Information (SI)	
Demographics and Baseline Characteristics	All Treated Analysis Set
Disease Characteristics	All Treated Analysis Set
Transplant History	All Treated Analysis Set
Discontinuation of Study Drug	All Treated Analysis Set
Terminated from Study	All Treated Analysis Set
Subjects Excluded from the Analysis set	All Treated Analysis Set
Duration, Cumulative Dose and Dose Intensity	All Treated Analysis Set
Study Drug Administration	All Treated Analysis Set
Major Protocol Deviation	All Treated Analysis Set
Prior cGVHD Therapy	All Treated Analysis Set
Concomitant Medications	All Treated Analysis Set
Concomitant Use of CYP3A Inhibitors	All Treated Analysis Set
Concomitant Use of CYP3A Inducers	All Treated Analysis Set
Concomitant Additional Immunosuppressants during Study	All Treated Analysis Set
Anti-coagulants	All Treated Analysis Set
Anti-platelets	All Treated Analysis Set
Potential Hy's Law Case	All Treated Analysis Set
Subsequent cGVHD Therapy	All Treated Analysis Set
Medical History	All Treated Analysis Set
Underlying Disease	All Treated Analysis Set
cGVHD Assessment (NIH)	All Treated Analysis Set
Efficacy (EF)	
Efficacy Variables	All Treated Analysis Set
cGVHD Response	All Treated Analysis Set
Corticosteroid requirement	All Treated Analysis Set
Symptom burden measured by the Lee cGVHD Symptom Scale	All Treated Analysis Set
Safety (SF)	
Treatment-emergent Adverse Events	Safety Analysis Set
Serious Adverse Events	Safety Analysis Set
Treatment-emergent Adverse Events Leading to Death	Safety Analysis Set
Treatment-emergent Adverse Events Leading to Discontinuation of Study Drug	Safety Analysis Set
Treatment-emergent Adverse Events Leading to Dose Reduction	Safety Analysis Set
Death	Safety Analysis Set
Laboratory Data	Safety Analysis Set
Vital Signs	Safety Analysis Set
Karnofsky/Lansky Performance Scale	Safety Analysis Set
Chimerism test	Safety Analysis Set
Pharmacokinetic (PK)	
Individual Plasma Ibrutinib Concentrations	Pharmacokinetic-evaluable Population
Ibrutinib pharmacokinetic parameters on Week 1, Day 1	Pharmacokinetic-evaluable Population
Ibrutinib pharmacokinetic parameters on Week 2, Day 1	Pharmacokinetic-evaluable Population
Individual Plasma PCI-45227 Concentrations	Pharmacokinetic-evaluable Population

Output Title	Analysis Set
PCI-45227 pharmacokinetic parameters on Week 1, Day 1	Pharmacokinetic-evaluable Population
PCI-45227 pharmacokinetic parameters on Week 2, Day 1	Pharmacokinetic-evaluable Population
Other (OT)	
Lot Number	All Treated Analysis Set