Janssen Pharmaceutical K.K. *

Statistical Analysis Plan

Phase 2 Study of Bruton's Tyrosine Kinase (BTK) inhibitor, Ibrutinib (PCI-32765) in Combination With Rituximab, in Japanese Patients With Waldenstrom's Macroglobulinemia (WM)

Protocol 54179060WAL2002; Phase 2

JNJ-54179060 (ibrutinib)

*This study is being conducted by Janssen Pharmaceutical K.K. in Japan.

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

TABLE OF CONTENTS

AMENDMENT HISTORY

SAP Version	Issue Date	Changes
Ver.1.0	09 December 2019	Not Applicable
Ver.2.0	03 September 2021	In the Section 2.9, imputation Rules for missing date of initial diagnosis, date of death and prior, concomitant and subsequent therapies are added. Section title changed by addition. The Section 4.5 of Prior Medication is added. The Section 4.7 of Prior WM therapies is added. In the Section 5.2.2, for ease of understanding, one-sided p-value of test for ORR is added. Waterfall plot for best reduction of serum IgM, swim lane plot is added, moreover summary of IgM values and change from baseline values by scheduled time points is added. In the Section 5.3.1, the censoring rule of PFS is clarified in the table for ease of understanding. In Section 5.3.2 of MYD88 and CXCR-4 description, following wording is added. *The following analysis for MYD88 and CXCR-4 may be shown in the separate report.* In Section, 5.4.1, TTR description, the wording is organized for clarification, and “time to best response” is removed for correction reason. In Section, 5.4.1, for DOR description and Sustained Hemoglobin Improvement description, the wording is organized for clarification. In Section 5.5, for ORR analysis by MYD88 and CXCR-4 categories, modified the description to declare the result may be reported in a separate report. In Section 6.1, the description is organized to clarify. In the Section 6.1.2, Rash, Cardiac failure have been added. The Section 6.4 of ECOG summary table is deleted.

ABBREVIATIONS

AE	adverse event
CI	confidence interval
CR	complete response
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
DPS	Data presentation specification
ECG	Electrocardiogram
ECOG	European cooperative oncology group
EOT	End of treatment
ICF	informed consent form
IRC	independent review committee
IV	intravenous
IWWM	International workshop on Waldenström's Macroglobulinemia
MedDRA	Medical Dictionary for Regulatory Activities
MR	Minimal response
NCCN	National Comprehensive Cancer Network
NCI CTCAE	National cancer institute common terminology criteria for Adverse Events
ORR	Overall response rate
PD	pharmacodynamic
PFS	Progression free survival
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	standardized MedDRA queries
TEAE	treatment-emergent adverse event
VGPR	Very good partial response
WHO	World Health Organization
WHO-DD	World Health Organization Drug Dictionary
WM	Waldenstrom's Macroglobulinemia

1. INTRODUCTION

This Statistical Analysis Plan (SAP) contains definitions of analysis sets, derived variables and statistical methods for analyses of efficacy, safety, pharmacokinetic (PK) and pharmacodynamics (PD) data of study 54179060WAL2002.

1.1. Trial Objectives

Objectives	Endpoints
Primary	
To evaluate ORR by IRC assessment, when combined with rituximab in Japanese participants with treatment naïve or relapsed/refractory WM.	The ORR is defined as the proportion of participants with CR, VGPR, or PR (ie, ≥PR) by IRC assessment. Response will be defined by the modified sixth IWWM (NCCN version 2, 2019)
Secondary	
To assess PFS by IRC assessment.	PFS is defined as duration from the date of initial dose of ibrutinib to the date of disease progression or death, whichever occurs first.
To determine the PK of ibrutinib in combination with rituximab in Japanese participants with treatment naïve or relapsed/refractory WM.	PK parameters of ibrutinib and metabolite PCI-45227 (if possible and judged relevant).
To explore biomarkers identified from other studies of ibrutinib in samples collected for MYD88 and CXCR-4 assessments.	Prognostic biomarkers relative to disease and/or treatment outcomes including MYD88 and CXCR-4.
To evaluate safety of ibrutinib, when combined with rituximab in Japanese participants with treatment naïve or relapsed/refractory WM.	Safety parameters of ibrutinib, including AEs and clinical laboratory assessments.

1.2. Trial Design

This is an open-label, single arm, multicenter Phase 2 study to evaluate the efficacy and safety of ibrutinib 420 mg in combination with rituximab in Japanese participants (≥20 years of age) with treatment naïve or relapsed/refractory WM.

The primary efficacy endpoint is ORR by IRC assessment in Japanese participants with treatment naïve or relapsed/refractory WM when ibrutinib is combined with rituximab. Overall response rate is defined as the proportion of participants who achieve CR, VGPR, or PR according to modified sixth IWWM (NCCN version 2, 2019).

The treatment phase will extend from first dose of ibrutinib until the EOT visit (which should occur after 30 days of last dose of ibrutinib or prior to the start of a new anticancer treatment). All participants will receive IV administration of rituximab weekly for 4 consecutive weeks, followed by a second course of IV rituximab administered weekly for 4 consecutive weeks after a 12-week interval. All participants will receive oral ibrutinib daily and continuously until criteria for permanent discontinuation of ibrutinib are met. Response assessments will be performed using the modified consensus criteria adapted from the sixth IWWM. Participants with confirmed PD must discontinue the study intervention.

A clinical cutoff of the primary endpoint, ORR (≥PR), will be conducted at the time when all the participants complete assessment of Week 57 or EOT visit. The response evaluable population is defined as all enrolled participants who have measurable disease at baseline, received at least 1

dose of ibrutinib, and have at least 1 adequate postbaseline disease assessment for responses (consecutive assessments are required for the CR, VGPR, PR, and MR except radiology assessment and bone marrow). Adequate disease assessment is defined as having sufficient evidence to correctly indicate that progression has or has not occurred. Participants who died due to progression are also considered to have had adequate assessment. At the same time, secondary endpoints will be evaluated.

1.3. Statistical Hypotheses for Trial Objectives

The primary hypothesis of this study is that ibrutinib in combination with rituximab is an effective agent in Japanese participants with treatment naïve or relapsed/refractory WM as measured by an ORR (the lower bound of exact 95% CI based on binomial distribution >32%).

1.4. Sample Size Justification

The target sample size is 14. Assuming an expected ORR of 72%, 14 participants are needed to demonstrate that the lower limit of exact 2-sided 95% CI of estimated ORR exceeds 32% with 80% power. The sample size was decided based on the study PCYC-1127-CA results, where the response rate was 72% for the ibrutinib plus rituximab arm, and 32% for the placebo plus rituximab arm.

1.5. Randomization and Blinding

Not Applicable.

2. GENERAL ANALYSIS DEFINITIONS

For continuous variables, number of observations, means, standard deviations, medians, and ranges will be included. For categorical variables, frequency and percentage will be summarized. For time-to-event variables, Kaplan-Meier estimates will be provided.

All tests will be conducted at a 2-sided alpha level of 0.05, and 95% CIs will be provided, unless stated otherwise.

2.1. Visit Windows

For visit-wise analysis, CRF-record visits will be followed. The visit windows are described in “Schedule of Activities” of the protocol.

For over the study period summary (eg, markedly abnormal values), unscheduled visit results will be included.

2.2. Analysis Sets

2.2.1. Enrolled Population

All participants who sign the ICF.

2.2.2. Safety / All Treated Analysis Set

All enrolled participants who receive at least 1 dose of ibrutinib.

2.2.3. Response Evaluable Analysis Set

All enrolled participants who have measurable disease at baseline, receive at least 1 dose of ibrutinib and who have at least 1 adequate postbaseline efficacy assessment.

2.2.4. Pharmacokinetics Evaluable Analysis Set

All enrolled participants who have received at least 1 dose of ibrutinib and have at least 1 post-dose PK sample obtained.

2.3. Study Day and Relative Day

Study Day 1 or Day 1 refers to the start of the first study drug administration. All 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 Day 1) +1, if visit date is ≥date of Day 1
- Visit date - Date of Day 1, if visit date <date of Day 1

There is no 'Day 0'.

2.4. Baseline

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

2.5. 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.

2.6. 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.

2.7. Dose Intensity

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

2.8. Relative Dose Intensity

Relative dose intensity (%) is defined as the percentage of total cumulative dose administered versus the total expected dose. Total cumulative dose administered is the sum of daily dose taken over the whole study course; and total expected dose is the product of the duration of the treatment

(day) and the protocol assigned daily dose. Relative dose intensity is calculated by total cumulative dose administered / total expected dose ×100%.

2.9. Imputation Rules for Missing Date

In general, imputation of missing dates will be made for AE onset date, AE end date, date of death, date of initial diagnosis, start and end dates of prior, concomitant and subsequent therapies. Start date will be imputed before end date.

- If the date is completely missing, no imputation will be made.
- If the year is missing, 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 day of the month will be used.

The above imputations will be modified by the following rules:

- For initial diagnosis if such imputed date is on or after the date of first dose of ibrutinib, then the date of first dose of ibrutinib - 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.
- If the imputed date is for a date of death and is before the last date that the subject is known to be alive, the latter date will be used.

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.
  - 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 year and month 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

The items of demographic and baseline characteristics presented in below table will be summarized using the all treated analysis set.

Continuous Variables:	**Summary Type**
Age (years)	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum].)
Weight (kg)	
Height (cm)	
Body surface area (m^2)	
Serum IgM (g/L)	
Beta-2 microglobulin (mg/L)	
Monoclonal protein spike (g/L)	
Hemoglobin (g/L)	
Platelets count (10^9 / L)	
Absolute neutrophil count (10^9 / L)	
Months from initial diagnosis to first dose of Ibrutinib	
Categorical Variables	**Summary Type**
Sex (male, female, unknown, undifferentiated)	Frequency distribution with the number and percentage of subjects in each category.
Age (<=65, >65; <=75, >75)	
Serum IgM (g/L) (<=70, >70)	
Beta-2 microglobulin (mg/L) (<=3, >3)	
Hemoglobin (g/L) (<=110, >110)	
ECOG status of baseline (0,1,2)	
Number of prior WM related therapies on CRF	
IPSS risk category	
Lymphadenopathy (Yes, No)	
Splenomegaly (Yes, No)	

Body surface is calculated as (weight in kg ^0.425 x height in cm ^0.725 x 71.84)/10000.
Here, baseline of IgM is the latest value which is observed before initiation of Ibrutinib but the observation which observed within after 35 days from WM plasmapheresis usage is excluded.

Listings of Demographics data will be provided.

4.2. Disposition Information

The number of subjects in the following disposition categories will be summarized throughout the study using Enrolled Population:

- Subjects Enrolled (participants who signed to IC)
- Subjects Screened
- Subjects Not treated
  - Analysis Sets (number of participants in each analysis set)

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

- Subjects completed the study
- Subjects ongoing study participation (including follow up period)
- Subjects who terminated study prematurely
  - Reasons for termination of study
- Ibrutinib disposition
  - Ongoing / Discontinued
  - Primary reason for discontinuation of study treatment
- Rituximab disposition
  - Completed / Ongoing / Discontinued
  - Primary reason for discontinuation of study treatment

Listings of subjects will be provided for the following categories:

- Subjects who terminated study prematurely
- Listing of Subjects who discontinued Study drug
- Subjects who are excluded from the analysis set

4.3. Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and summarized by SOC and PT using all treated analysis set. In addition, medical history will be listed.

4.4. Concomitant Medications

Concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO-DD).

Summaries of concomitant medications will be presented by therapeutic class and preferred term using all treated analysis set. The proportion of subjects who receive each concomitant medication will be summarized as well as the proportion of subjects who receive at least 1 concomitant medication. The same analysis for Concomitant CYP3A inhibitors, for Concomitant CYP3A inducers will be performed respectively.

Listing of prior and subsequent WM related-therapies and listing of concomitant medications will be created.

4.5. Prior Medications

Prior medications will be coded using the World Health Organization Drug Dictionary (WHO-DD).

Summaries of concomitant medications will be presented by therapeutic class and preferred term using all treated analysis set. The proportion of subjects who receive each concomitant medication will be summarized as well as the proportion of subjects who receive at least 1 concomitant medication.

Listing of Prior Medications will be provided.

4.6. Extent of Exposure

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

- Treatment duration (months)
  - (date of last dose of study drug – date of first dose of study drug + 1 day) / 30.4375.
- Cumulative total dose of ibrutinib (mg)
- Cumulative total dose of rituximab (mg/m^2)
- Dose intensity of ibrutinib (mg/day)
  - Dose intensity is calculated as (sum of total daily dose during the treatment phase)/study drug duration.
- Dose intensity of rituximab (mg/m^2/week)
  - Dose intensity is calculated as (sum of total dose during the treatment phase)/number of weeks in which rituximab is administrated
- Relative dose intensity of ibrutinib (%)
- Relative dose intensity of rituximab (%)
- Relative dose intensity is calculated by total cumulative dose administered / total expected dose ×100%.
- Number of infusion received of Rituximab.
- Time on Study (month)

– (study exit date/last known alive date – date of first dose of study drug + 1 day)/30.4375.

For each study drug, incidence and frequency of dose interruption and reasons of dose interruption will be summarized. In addition, the incidence of dose interruption (any dose skip with 7 days or more), the incidence of any dose reduction (at least one reported dose reduction) and the reason of dose reduction will be summarized for ibrutinib.

Listing of subject treatment duration, cumulative dose and dose intensity and relative dose intensity is provided.

Listing of study drug administration is provided.

4.7. Prior WM Therapies

Summary of prior WM Therapies will be presented using all treated analysis set. In the analysis descriptive statistics of time from last treatment (Interval between the last date of last prior treatment and first dose of Ibrutinib) and number of prior WM therapies are calculated.

4.8. Protocol Deviations

In general, protocol 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 using all treated analysis set.

A corresponding listing is also provided. COVID-19 related protocol deviations will be provided in a separate listing.

5. EFFICACY

5.1. Analysis Specifications

5.1.1. Level of Significance

All tests will be conducted at a 2-sided alpha level of 0.05, and 95% CIs will be provided, unless stated otherwise.

5.1.2. Data Handling Rules

There is no imputation planned for missing efficacy endpoint value.

5.2. Primary Efficacy Endpoint(s)

Overall response rate is defined as the proportion of participants who achieve ≥PR according to the modified sixth IWWM (NCCN version 2, 2019).

5.2.1. Definition

ORR:

Proportion of participants achieving a best overall response of confirmed CR, VGPR, or PR by IRC assessment at or prior to initiation of subsequent antineoplastic therapy.

5.2.2. Analysis method

The response evaluable analysis set will be used for analysis of primary endpoint. And, all treated analysis set will be used for supplementary analysis.

The number of subjects who experienced response, the ORR and its 95% confidence interval (CI) will be calculated with the exact test for binomial distribution. The study is considered as positive if the lower limit of the exact 2-sided 95% CI based on binominal distribution exceeds the threshold value (0.32). In addition, best overall response will also be summarized. And one-sided p-value will be displayed.

In addition, waterfall plot for best reduction in %change from baseline of serum IgM using response evaluable analysis set and swim lane plot by IRC Assessment using response evaluable analysis set will be provided, and IgM values and change from baseline values will be summarized as descriptive statistics by scheduled time points. Here, baseline of IgM is the latest value which is observed before initiation of Ibrutinib but the observation which observed within after 35 days from WM plasmapheresis usage is excluded. And, the IgM values which are observed within after 35 days are excluded from the calculation of %change from baseline and change from baseline.

5.3. Secondary Endpoints

The secondary efficacy endpoints are:

- Progression-free survival (PFS)
- Pharmacokinetics (PK) profile of ibrutinib and metabolite PCI-45227 (detailed analysis plan is described in Section 7)
- Prognostic biomarkers relative to disease and/or treatment outcomes including MYD88 and CXCR-4

5.3.1. Definition

PFS:

Time from the date of initial dose to the date of first documented evidence of PD, death, or date of censoring whichever occurs first, regardless of the use of subsequent antineoplastic therapy prior to documented PD or death [date of first PD or death or censoring−date of initial dose+1 day]. Participants whose diseases have not progressed and who are still alive at the end of the study or clinical cutoff will be censored at the last adequate disease assessment. Participants who do not have any postbaseline disease evaluation will be censored at the date of the first dose of Ibrutinib.

The censoring method is descried as below.

PFS Event and Censoring Method

Situation	Date of Progression or Censoring	Outcome
Disease progression	Earliest date that indicates disease progression	PFS event
Death	Date of death	PFS event
No postbaseline disease assessment	First dosing date	Censored
Other (eg, withdrawal of consent to study participation, lost to follow-up etc.)	Date of last disease assessment prior to withdrawal of consent to study participation, lost to follow-up	Censored

5.3.2. Analysis Methods

The all treated analysis set will be used for all secondary efficacy endpoints.

PFS:

The Kaplan-Meier method will be used to descriptively summarize the PFS in the all treated analysis set. Median PFS and the corresponding 95% CI will be provided if estimable with Kaplan-Meier plot. In addition, Kaplan-Meier estimates for PFS at 6, 12, 18 month and its CIs are provided.

MYD88 and CXCR-4:

The following analysis for MYD88 and CXCR-4 may be shown in the separate report.

Frequency distribution with the number and percentage of subjects in each category of MYD88, CXCR-4, combination status of MYD88 and CXCR-4 will be provided.

- MYD88
- CXCR-4
- MYD88 /CXCR-4
  - Combination of status of MYD88 and CXCR-4

5.4. Exploratory Endpoints

- Time to response (TTR)
- Duration of response (DOR) for responders (≥PR)
- Clinical response rate (CRR)
- Sustained Hgb improvement
- Time to next treatment (TTNT)
- Overall survival (OS)

5.4.1. Definition

TTR:

Time to initial response is the time from the date of initial administration of ibrutinib to the date of initial documentation of an IRC assessed response (≥PR) in a participant who responded. Time to response is the time from the initial administration of ibrutinib to the date of achieving initial response [date of first response−date of initial administration of ibrutinib +1 day]. TTR is calculated based on the IRC assessment at or prior to initiation of subsequent antineoplastic therapy and TTR is defined for responders only.

DOR:

Duration from the date of initial documentation of an IRC assessed response (≥PR), to the date of first documented evidence of PD, death, or date of censoring if applicable whichever occurs first. DOR is defined for responders only [date of first PD or death or censoring−date of first response+1 day]. The same censoring rules for PFS are used for DOR.

CRR:

Proportion of participants achieving a best overall response (≥MR) at or prior to initiation of subsequent antineoplastic therapy.

Sustained Hemoglobin Improvement:

Hemoglobin improvement is defined as achieving an increase of ≥2 g/dL over baseline at or prior to initiation of subsequent antineoplastic therapy regardless of baseline value. And it is also defined as achieving an increase to >11 g/dL with an increase of ≥0.5 g/dL over baseline at or prior to initiation of subsequent antineoplastic therapy for participants with baseline is ≤11 g/dL.

The Sustained Hgb improvement is defined as that sustaining hemoglobin improvement continuously for ≥56 days (8 weeks) without blood transfusion in the duration of sustaining hemoglobin improvement (Blood cell/whole blood transfusions, Platelet transfusions).

TTNT

Time-to-next treatment is measured from the date of the date of initial dose of ibrutinib to the start date of any subsequent systematic therapy for WM. Subject without subsequent systematic therapy will be censored at the date of last contact.

OS

Overall survival (OS) is measured from the date of initial dose of ibrutinib to the date of death due to any cause. Subjects who are lost to follow-up will be censored at the time of lost to follow-up. Subjects who are still alive at the clinical cut-off date for the analysis will be censored at the last known alive date. The date of last known alive will be determined by the maximum collection/assessment date from among selected data domains within the clinical database.

In addition, unless specify, disease evaluation is based on the independent review committee (IRC).

5.4.2. Analysis Methods

The all treated analysis set will be used for all exploratory endpoints.

TTR:

Time to response (time to initial response) will be summarized by descriptive statistics. Analysis is performed using only subjects who achiever PR or better in the all treated analysis set.

DOR:

The DOR will be calculated by the Kaplan-Meier method descriptively in participants who responded. Median DOR and the corresponding 95% CI will be provided if estimable with Kaplan-Meier plot.

CRR:

The CRR will be analyzed in the same manner as ORR.

Sustained Hemoglobin Improvement:

Proportion and its exact 95% CI will be calculated for all participants who achieved sustained improvement and for these participants with ≤11 g/dL baseline value.

TTNT:

TTNT will be analyzed using similar statistical methods as PFS analysis.

OS:

OS will be analyzed using similar statistical methods as PFS analysis.

5.5. Other exploratory analysis

ORR is summarized by with and without prior systematic therapy of WM using all treated analysis set.

The same analysis may be performed by MYD88 categories and by CXCR-4 categories, and the result may be reported in a separate report.

6. SAFETY

The safety analysis will be performed on the 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 intervention through the day of last dose plus 30 days is considered to be treatment-emergent.

If the event date is recorded as partial or completely missing, then the event will be considered as 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 as 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 as 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.

All reported treatment-emergent adverse events (TEAEs) will be included in the analysis and summarized by system organ class (SOC) and preferred term (PT). For each adverse event, the number of events, and the number and percentage of subjects who experience at least 1 occurrence of the event will be summarized.

Summary tables will be provided for:

- Overall Summary of TEAE
- TEAEs by System Organ Class (SOC), preferred term (PT) and toxicity (All, Grade 3 or Higher)
- Serious TEAEs by SOC, PT and toxicity (All, Grade 3 or Higher)
- TEAEs with frequency of at least 10% by System Organ Class (SOC), preferred term (PT) and toxicity (All, Grade 3 or Higher)
- TEAEs leading to discontinuation of Ibrutinib by SOC, PT and toxicity (All, Grade 3 or Higher)
- TEAEs leading to discontinuation of Rituximab by SOC, PT and toxicity (All, Grade 3 or Higher)
- TEAEs leading to dose reduction of Ibrutinib by SOC, PT and toxicity (All, Grade 3 or Higher)
- TEAEs leading to interruption of Ibrutinib by SOC, PT and toxicity (All, Grade 3 or Higher)
- TEAEs leading to interruption of Rituximab by SOC, PT and toxicity (All, Grade 3 or Higher)
- TEAEs by System Organ Class (SOC), preferred term (PT) and relation to drugs (All, related to Ibrutinib, related to Rituximab, related to at least one drug) and toxicity (All, Grade 3 or Higher)
- TEAEs leading to death by SOC, PT
- TEAEs by SOC, PT and period (total, < 16 Weeks, 16<= - <32 Weeks, =>32 Weeks)

In addition, listings will be provided as appropriate.

6.1.1. AEs of special interest (AESI)

Number and percent of subjects with following AESIs will be summarized by SOC, PT and toxicity (All, Grade 3 or Higher). The detailed definition of AESIs will be described in Data Presentation Specification (DPS) created separately as necessary.

Major hemorrhages

Major hemorrhage is defined as any of the following:

1. Any treatment-emergent hemorrhagic AEs of ≥Grade 3 (Note: All hemorrhagic events requiring transfusion of red blood cells should be reported as ≥Grade 3 AE per NCI-CTCAE. Those events meeting the definition)
2. Any treatment-emergent SAEs of bleeding of any grade
3. Any treatment-emergent central nervous system hemorrhage/hematoma of any grade.

Here, central nervous system hemorrhage/hematoma is selected using the rule below.

Step 1.

Define three subsets of events

Subset A: PTs in the "Central nervous system haemorrhages and cerebrovascular conditions (SMQ)"

Subset B: PTs in the "Nervous system disorders" (SOC)

Subset C: PTs in the "Haemorrhage terms (excl laboratory terms) (SMQ)" narrow scope.

Step 2.

Identifying any PTs that are in (Subset A or Subset B) and Subset C as central nervous system hemorrhage/hematoma events.

Other Malignancies

Treatment-emergent Neoplasms benign, malignant and unspecified (incl cysts and polyps) of any grade (SOC).

6.1.2. Other safety observations

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

Hemorrhagic event

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

Leukostasis

Obtained for preferred term of "leukostasis syndrome".

Hypersensitivity

This definition will be specified in DPS, separatory.

Eye Disorders

Obtained from the SOC of “Eye Disorders”.

Hepatic Disorders

Obtained from the SOC of “Hepatobiliary Disorders”.

Tumor Flare (IgM flare)

The Medical Dictionary for Regulatory Activities (MedDRA) does not support the reporting of “IgM flare” and therefore these events should be reported as an adverse event of 'tumor flare'. Therefore, in this analysis, the events which reported by the term “tumor flare” will be summarized.

Infusion-related Reactions

The adverse event which reported as an infusion reaction associated with Rituximab.

Cytopenic Adverse Events

Obtained from preferred terms of “neutropenia”, “febrile neutropenia”, “thrombocytopenia”, and “anaemia”.

Cardiac arrhythmia

Cardiac arrhythmias (SMQ, broad and narrow) after excluding atrial fibrillation (PT) terms. In addition, Ventricular tachyarrhythmias (SMQ, narrow) will be summarized separately.

Cardiac failure

Cardiac failure: Cardiac failure SMQ (narrow).

Interstitial Lung Disease

Interstitial Lung Disease (ILD) will be determined based on Interstitial lung disease (SMQ, narrow).

Hypertension

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

Infections

Obtained from the SOC of “Infection and Infestations”

Tumor Lysis syndrome

Obtained from preferred term of “tumour lysis syndrome”

Ischemic stroke

Ischemic central nervous system vascular conditions (SMQ)

Rash

All PTs containing the word "rash".

6.2. Clinical Laboratory Tests

All clinical laboratory tests will be summarized using safety analysis set. Applicable laboratory results will be graded according to NCI-CTCAE Version 4.03.

For continuous variables, the observed values will be summarized as descriptive statistics by scheduled time points, in addition, change from baseline values will be summarized in the same manner.

Frequency of the changes from baseline results will be presented in pre versus postintervention by scheduled time points as cross-tabulations (with classes for Low, Normal, and High).

For laboratory items, the worst post baseline grades will be summarized.

Change from baseline to the worst grade experienced by the subject during the study will be provided as shift tables.

In addition, the summary table for liver function abnormalities based on liver function based on ALT, AST, ALP and TB values will be provided.

A listing of participants with any laboratory results outside the reference ranges will be provided.

A listing of subjects with laboratory results will be provided.

6.3. Vital Signs and Physical Examination Findings

Continuous vital sign items including weight, blood pressure, pulse rate, respiratory rate, and body temperature will be summarized by each time point. In addition, change from baseline values are summarized by each time point for each vital sign item.

Moreover, a data listing by subjects will be presented.

6.4. ECOG status

A data listing for ECOG values by subjects will be provided.

6.5. Electrocardiogram

The result of 12 Lead standard ECG observed at screening phase is summarized using the safety analysis set. The items which are summarized are below.

Overall interpretation (Normal, Abnormal (Clinically Significant, Not Clinically Significant), Not Evaluable)

In addition, the list of all ECG results (screening phase and unscheduled evaluation) are created.

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, AUC_{last}, AUC_{24}, and λ_Z) of ibrutinib and PCI-45227 will be calculated using noncompartmental analysis based on actual sampling times. Metabolite-to-parent ratio (MPR) based on C_{max}, AUC_{last}, and AUC_{24} 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}, AUC_{last}, AUC_{24},, dose-normalized C_{max}, AUC_{last}, and AUC_{24}, MPR based on C_{max}, MPR based on AUC_{last}, MPR based on AUC_{24}) 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 may be performed on the individual PK parameters of ibrutinib and PCI-45227 (C_{max}, t_{max}, $t_{1/2}$, t_{last}, CL/F, AUC_{last}, AUC_{24}, and λ_Z). Necessity of subgroup analysis will be determined based on the actual number of subjects who received concomitant CYP3A inhibitors and/or dose reduction. 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, $t_{1/2}$, CL/F, and λ_z will be reported with annotation as such and excluded from the descriptive statistics.
  - At least 3 data points not including C_{max} 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.

LISTINGS

All Listings which will be provided in this statistical analysis plan is below.

- Listing of Subjects Who Discontinued Study drug
- Listing of Subjects With Major Protocol Deviations
- Listing of Subjects With Protocol Deviations Related to COVID-19
- Listing of Subjects Who Terminated Study Participation Prematurely
- Listing of Subjects Who are excluded from the analysis set
- Listing of Medical history
- Listing of WM disease history
- Listing of Prior Medications and Concomitant Medications
- Listing of Prior WM systematic therapies
- Listing of Prior WM Plasmapheresis/Transfusion
- Listing of Prior WM Radiotherapy
- Listing of Subsequent Systematic Therapies
- Listing of subsequent Radiotherapy
- Listing of Demographics and Baseline Characteristics
- Listing of IPSS risk category and reason for Initiating WM treatment
- Listing of Study drug Administration
- Listing of treatment duration, cumulative dose, dose intensity
- Listing of Efficacy Variables
- Listing of Disease progression for WM by investigator
- Listing of ECOG Values
- Listing of New malignancies
- Listing of Bone marrow for aspirate/biopsy for WM
- Listing of Laboratory Values
- Listing of participants with any laboratory results outside the reference ranges
- Listing of local efficacy lab results of Beta 2 microglobulin
- Listing of Subjects with IgM result
- Listing of Subjects with liver function abnormality at any time point
- Listing of Vital Signs
- Listing of ECG Values
- Listing of death information

- Listing of TEAEs
- Listing of Serious TEAEs
- Listing of TEAEs leading to dose reduction
- Listing of TEAEs leading to discontinuation of study drug
- Listing of TEAEs leading to death
- Listing of TEAEs leading to drug interruption
- Listing of lot number of study drug
- Individual Plasma concentrations of ibrutinib and PCI-45227
- Pharmacokinetic parameters of Ibrutinib and PCI-45227

CHANGE OF ANALYSIS PLAN FROM PLANNED IN PROTOCOL

The tables in this section lists the analyses which were planned in the protocol but not conducted or modified in the SAP.

Section in the protocol	Description in SAP	Reason
Section 9.4.4. Clinical Laboratory Tests "Reference ranges and markedly abnormal results (specified in the SAP) will be used in the summary of laboratory data." "A listing of participants with any markedly abnormal laboratory results will also be provided."	None	Because the number of patients is small. The information of laboratory tests can be obtained easily from summary table and list of laboratory tests.
Section 9.4.4. Vital Signs "The percentage of participants with values beyond clinically important limits will be summarized."	None	Because the number of patients is small. The information of vital signs can be obtained easily from summary table and list of vital signs.
Section 9.4.4. In general, continuous variables will be summarized using descriptive statistics (n, mean, median, standard deviation, standard error and range).	descriptive statistics is (N, mean, standard deviation [SD], median and range [minimum and maximum].)	For summarizing the safety outcome data and for grasping the data distribution, n, mean, median, standard deviation are sufficient. Standard error is omitted.