Janssen Research & Development

Statistical Analysis Plan

A Single Arm, Multicenter, Phase 4 Study of the Bruton's Tyrosine Kinase (BTK) Inhibitor, ibrutinib (PCI-32765) in Chinese Subjects with Relapse or Refractory Waldenström's Macroglobulinemia

Protocol 54179060WAL4001; Phase 4

JNJ-54179060 (ibrutinib)

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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 History Summary

SAP Version	Approval Date	Major Changes
1	25 September 2020	Not Applicable
2	22 April 2022	Added analysis of primary estimand (section 5.2.3). In section 6.1.1., added Eye Disorders and Other Malignancies in AEs of special interest (AESI). In section 6.1.2., added Cardiac failure, Leukostasis, Hepatic Disorders, Cytopenic Adverse Events, Infections, Tumor Lysis syndrome, Ischemic stroke, Rash. And Other Malignancies has been removed. In section 7, the wording is organized to clarify.

ABBREVIATIONS

AE	adverse event
BQL	below the quantification limit
CCO	clinical cutoff
CI	confidence interval
CR	complete response
CRF	case report form
CRR	clinical response rate
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
IWWM	International Workshop on WM
MedDRA	Medical Dictionary for Regulatory Activities
MR	minor response
ORR	overall response rate
OS	overall survival
PD	progression disease
PFS	progression-free survival
PI	principal investigator
PK	pharmacokinetic(s)
PR	partial response
PT	preferred term
SAE	serious adverse event

SAP	Statistical Analysis Plan
SD	standard deviation
SMQs	standardized MedDRA queries
SOC	system organ class
TEAE	treatment-emergent adverse event
TTR	time to response
VGPR	very good partial response
WHO	World Health Organization
WHO-DD	World Health Organization Drug Dictionary
WM	Waldenström's Macroglobulinemia

1. INTRODUCTION

This Statistical Analysis Plan (SAP) covers Primary Analysis and Final Analysis specified in the protocol 54179060WAL4001. It contains definitions of analysis sets, derived variables and statistical methods for analyses of efficacy, safety and pharmacokinetic (PK) data of study 54179060WAL4001.

1.1. Trial Objectives

Primary Objective

The primary objective of this study is to evaluate the efficacy of ibrutinib based on overall response rate (ORR) (partial response [PR] or better) by investigator assessment per the modified Consensus Response Criteria from the VIth International Workshop on Waldenström's Macroglobulinemia (IWWM) (NCCN 2019)[1,2], in Chinese subjects with relapsed or refractory Waldenström's Macroglobulinemia (WM).

Secondary Objectives

Secondary objectives are to evaluate: clinical response rate (minor response [MR] or better) by investigator assessment according to the modified VIth IWWM (NCCN 2019) criteria, Very Good PR (VGPR) or better by investigator assessment according to the modified VIth IWWM (NCCN 2019) criteria; duration of response (DOR) by investigator assessment; time to response (TTR) by investigator assessment; progression-free survival (PFS) by investigator assessment; overall survival (OS); safety and PK of ibrutinib in Chinese subjects with relapsed or refractory WM.

1.2. Trial Design

This is a single-arm multicenter, Phase 4 study to evaluate the efficacy and safety of ibrutinib in Chinese subjects with relapsed or refractory WM with symptomatic disease meeting at least 1 of the recommendations from the Second IWWM for requiring treatment.

Approximately 17 subjects will be enrolled into the study. Subjects will receive ibrutinib 420 mg daily until disease progression or unacceptable toxicity, whichever occurs first. Ibrutinib will be supplied as hard gelatin capsules for oral administration.

The study will include a Screening Phase, a Treatment Phase and a Follow-Up Phase. During the Screening Phase, the subjects' eligibility will be determined. The Treatment Phase will extend from first dose of study drug until study drug discontinuation. The Follow-up Phase will consist of the Post-treatment pre-disease progression Phase and a Post-disease Progression Phase. The Post-treatment pre-disease progression Phase will extend from the discontinuation of treatment (for reasons other than disease progression) until the subject has progressive disease, at which point the Post-disease Progression Phase will begin. Subjects who progress on treatment will transition directly to the post disease progression phase. In this latter phase, subsequent anticancer therapy, occurrence of any other malignancy and survival status will be recorded until death, lost to follow-up, consent withdrawal, or study closure. The study is planned to be completed 3 years after the last subject receives first dose.

Clinical cutoffs (CCOs) planned for this study are:

- CCO for the primary analysis is estimated to be performed approximately 12 months after the last subject receives first dose. Alternative appropriate cutoffs will be considered based on regulatory requirement.
- CCO for the final analysis is estimated to occur 3 years after last subject receives first dose.

1.3. Statistical Hypotheses for Trial Objectives

The primary hypothesis for this study is that ibrutinib is an effective agent as measured by ORR (with a point estimate approximately 70% and the lower bound of the 90% confidence interval [CI] is greater than 32%) in Chinese subjects with relapsed/refractory WM.

1.4. Sample Size Justification

Assuming the ORR (PR or better) by investigator is 69.8% in the study population, which is the same as global pivotal study (PCYC-1118E) result, approximately 17 subjects will be required to obtain at least 85% power to declare the ORR is 32% (the minimum clinically meaningful ORR) or higher at the 1-sided significance level of 0.05.

1.5. Randomization and Blinding

This is an open label study, randomization and blinding procedures are not applicable.

2. GENERAL ANALYSIS DEFINITIONS

2.1. Visit Windows

For visit-wise analysis, CRF-recorded visits will be followed.

The visit windows are described in “Time and Events Schedule” of the protocol.

2.2. Pooling Algorithm for Analysis Centers

Data from all study centers will be pooled for analyses.

2.3. Analysis Sets

2.3.1. All Treated Analysis Set

All Treated analysis set is defined as all enrolled subjects who receive at least 1 dose of study drug.

2.3.2. Safety Analysis Set

Safety analysis set is defined as all enrolled subjects who receive at least 1 dose of study drug. The safety population is identical to All Treated population.

2.3.3. Pharmacokinetics Evaluable Analysis Set

PK evaluable analysis set includes all enrolled subjects who receive at least 1 dose of ibrutinib and have at least 1 available PK sample after treatment.

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 prior to the start of the first study agent 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 drug is calculated as (sum of total daily dose during the treatment phase)/treatment 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 Date

In general, imputation of missing dates will be made for AE onset date, AE resolution date, start and end dates of prior and concomitant and subsequent therapies 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 presented 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 information 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

The number of subjects in each analysis set will be summarized.

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 Characteristic 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)	
Aspartate Aminotransferase (AST) (U/L)	
Alanine Aminotransferase (ALT) (U/L)	
Total bilirubin (umol/L)	
Baseline creatinine (umol/L)	
Baseline creatinine clearance rate (mL/min)	
Categorical Variables	
Age (<=65, and >65 years)	Frequency distribution with the number and percentage of subjects in each category.
Sex (male, female, undifferentiated)	
Baseline creatinine clearance rate (<30mL/min, 30-<60mL/min, >=60mL/min)	
Baseline liver function based on NCI criteria[a] (Normal, Mild, Moderate and Severe)	

Table 1: Demographic and Baseline Characteristic Variables

Continuous Variables:	Summary Type
a: Mild (total bilirubin ≤ ULN and AST > ULN) or (ULN < total bilirubin ≤ 1.5×ULN); moderate (1.5×ULN < total bilirubin ≤ 3×ULN); and severe (total bilirubin > 3×ULN).	

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

- Month from initial diagnosis, which is defined as the time period between date of initial WM diagnosis and date of first dose of study drug.
- ECOG performance grade (0-1, 2)
- Number of prior systemic treatment regimens (1-2, >-3)
- Serum IgM
- Monoclonal protein spike
- Beta-2 microglobulin
- Extramedullary disease (adenopathy, splenomegaly)
- Longest diameter of spleen
- Sum of products of diameters - target nodal lesions
- Tumor involvement of the bone marrow by: Cellularity
- Intertrabecular space (percentage of total bone marrow cells within intertrabecular space)
- Cytopenia (hemoglobin <=110 g/L, platelets <=100x10^9/L, absolute neutrophil count <=1.5x10^9/L)

4.2. Disposition Information

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

- Subjects screened
- Subjects received study agent
- Subjects who is still on treatment at CCO
- Subjects who discontinued study agent
- Reasons for discontinuation of study agent, including COVID-19 related reasons
- Subjects who terminated study prematurely
- Reasons for termination of study

Listings of subjects will be provided for the following categories:

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

Subjects who discontinue from treatment or study due to COVID-19 related reasons will be listed.

4.3. Extent of Exposure

Extent of exposure to study treatment will be summarized and presented based on the safety analysis set. Descriptive statistics (N, mean, SD, median, and range [minimum, maximum)) will be presented for the following parameters:

- Treatment duration (month)
- Cumulative total dose (g)
- Dose intensity (mg/day)
- Relative dose intensity
- Time on study (month)

The number (%) of subjects with a study drug modification (dose skip and/or dose reduction) will be summarized. Reasons for study drug modifications will also be summarized.

4.4. Protocol Deviations

In general, the following list of major protocol deviations may have the potential to impact subjects' rights, safety or well-being, or the integrity and/or result of the clinical study. Subjects with major protocol deviations (including COVID-19 related deviations) will be identified prior to database lock and the subjects with major protocol deviations will be summarized by category for all treated analysis set.

- Entered but did not satisfy inclusion/exclusion criteria
- Received a disallowed concomitant treatment
- Received incorrect dose
- Developed withdrawal criteria but not withdrawn
- Efficacy assessment deviation
- Safety assessment deviation

4.5. 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 drug. Concomitant medications are defined as any therapy used on or after the same day as the first dose of study drug, including those that started before and continue on after the first dose of study drug.

Summaries of prior and concomitant medications will be presented by therapeutic class and preferred term for all treated analysis set. In addition, the following concomitant medications will be summarized separately: growth factors, blood supportive products and immunoglobulin,

CYP3A inhibitors (strong, moderate and weak), CYP3A inducers, anticoagulants and/or antiplatelets and subsequent antineoplastic therapy.

In addition, concomitant medication for COVID-19 infection will be listed.

4.6. Medical history

Medical history collected at baseline or screening visit will be summarized by system-organ class and preferred term for all treated population.

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 0.05. For result presentation purpose, a 2-sided 90% 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 primary efficacy endpoint is ORR by investigator assessment.

5.2.1. Definition

ORR is defined as the proportion of subjects who achieve PR or better per the modified Consensus Response Criteria from the VIth IWWM (NCCN 2019).

5.2.2. Analysis Methods

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

The primary analysis for primary endpoint will be conducted at the time of approximately 12 months after the last subject receives first dose. Final analysis will be conducted at the study end, which is estimated to occur 3 years after last subject receives first dose.

The overall response rate (PR or better) and its 90% 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 90% confidence interval based on binominal distribution exceeds the threshold value (0.32).

5.2.3. Primary Estimand

Primary Trial Objective: To evaluate the efficacy of ibrutinib in Chinese patients with relapsed or refractory WM.

Primary Estimand Scientific Question of Interest: What is the effect on overall response rate of assigning ibrutinib to Chinese relapsed or refractory WM subjects?

The primary estimand, the main clinical quantity of interest to be estimated in the study, is defined by the following 5 components:

- **Population:** Chinese subjects with relapsed or refractory Waldenstrom's Macroglobulinemia who have received at least one prior therapy for Waldenstrom's Macroglobulinemia and have had either documented disease progression or had no response (stable disease) to the most recent treatment regimen.
- **Variable:** Overall response
- **Treatment:** Ibrutinib 420 mg orally, once daily
- **Summary measure:** Overall response rate
- **Intercurrent Events (IEs) and Corresponding Strategies:**

Intercurrent Events	**Name of Strategy for Addressing Intercurrent Events and Its Description**
Subsequent anti-cancer therapy	**While on Treatment Strategy**, targeting a treatment effect prior to the initiation of subsequent anti-cancer therapy.
Treatment discontinuation	**Treatment Policy Strategy**, targeting a treatment effect regardless of this IE.

5.3. Secondary Efficacy Endpoints

The secondary efficacy endpoints are:

- Clinical response rate (CRR, i.e. MR or better)
- Very good partial response (VGPR) or better rate
- Duration of response (DOR)
- Time to response (TTR)
- Progression-free survival (PFS)
- Overall survival (OS)

5.3.1. Definition

Clinical response rate:
CRR is defined as the proportion of subjects who achieve MR or better according to the modified

IVth IWWM (NCCN 2019) criteria as assessed by the investigator.

Very good partial response (VGPR) or better rate:
VGPR or better rate is defined as the proportion of subjects who achieve VGPR or better according to the modified IVth IWWM (NCCN 2019) criteria as assessed by the investigator.

Duration of response (DOR):
DOR is defined as duration from the date of initial documentation of a response (PR or better) to the date of first documented evidence of progressive disease, death or date of censoring if applicable, for responders (PR or better) as assessed by the investigator. DOR will be right censored based on Table 2 for all responders:

Table 2: Date of Event or Censoring for Duration of Response/Progression Free Survival

Situation	Date of DOR/PFS event or Censoring	Outcome
Death or disease progression occurred regardless of the use of subsequent antineoplastic therapy prior to documented death or disease progression.	Earliest date of adequate disease assessment documenting disease progression or date of death, whichever occurs first.	Event
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

Time to response:
Time to response is defined as the time from the date of first dose to the date of initial documentation of a response (PR or better) for responders.

Progression-free survival (PFS):
PFS is defined as duration from the date of first dose to the date of disease progression or death, whichever is first reported, assessed according to the modified VIth IWWM (NCCN 2019)

criteria. The same censoring rules for DOR are used for PFS.

Overall survival (OS):
OS is measured from the date of first dose to the date of the subject's death from any cause. OS will be right censored if no death has occurred at the data analysis cutoff date.

5.3.2. Analysis Methods

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

CRR rate and VGPR or better rate will be analyzed with the exact 2-sided 90% CI 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.

Time to response will be summarized descriptively for responders only.

Progression-free survival will be evaluated descriptively using Kaplan-Meier method. Median PFS and the corresponding 95% CI will be provided if estimable with Kaplan-Meier plot. PFS rates at 1-year, 2-year and 3-year landmarks will also be estimated using Kaplan-Meier.

OS will be evaluated in a similar fashion as DOR and PFS.

6. SAFETY

All safety analyses will be based on the safety analysis set and based on actual treatment received, unless otherwise specified.

For all continuous safety variables, descriptive statistics will include the N, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized using frequency counts and percentages.

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). Treatment-emergent adverse events (TEAEs) are those adverse events occurring after the first dose of study drugs and within 30 days following the last dose of study drug or initiation of subsequent antineoplastic treatment, whichever occurs earlier; any adverse event that is considered study drug-related regardless of the start date of the event; or any adverse event that is present at baseline but worsens after the first administration of study drug in severity or is subsequently considered drug-related by the investigator. If the event occurs on the day of the initial administration of study agent, and either event time or time of administration are missing, then the event will be assumed 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. 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 treatment-emergent adverse events:

- Overall summary of all 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 modification (including dose interruption and 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
- TEAEs leading to death by SOC and PT
- TEAEs by SOC, PT and toxicity by period
- TEAE of interest for COVID-19 infection by PT and toxicity grade
- Serious TEAE of interest for COVID-19 infection by PT and toxicity grade

- TEAE of interest for COVID-19 infection leading to death by PT

In addition to the summary tables, 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 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 bleeding of any grade
- Treatment-emergent central nervous system hemorrhage/hematoma of any grade

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

Eye Disorders

Eye disorders will be obtained from the SOC of "Eye Disorders".

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.

6.1.2. AEs of clinical interest

Cardiac arrhythmia

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

Cardiac failure

Cardiac failure will be determined based on Cardiac failure SMQ (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.

Leukostasis

Leukostasis will be obtained for preferred term of "leukostasis syndrome".

Hypertension

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

Hepatic Disorders

Hepatic disorders will be obtained from the SOC of "Hepatobiliary Disorders".

Cytopenic Adverse Events

Cytopenic adverse events will be obtained from preferred terms of "neutropenia", "neutrophil count decreased" "febrile neutropenia" , "thrombocytopenia" " platelet count decreased" and "anaemia".

Infections

Infections will be obtained from the SOC of "Infections and Infestations".

Tumor Lysis syndrome

Tumor Lysis syndrome will be obtained from preferred term of "tumor lysis syndrome".

Ischemic stroke

Ischemic central nervous system vascular conditions (SMQ).

Hypersensitivity

This definition will be specified in DPS, separatory.

Rash

All preferred terms containing the word "Rash".

6.2. 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 hematocrit
- Chemistry: calcium, sodium, potassium, glucose, total bilirubin, blood urea nitrogen (BUN), creatinine, total protein, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, phosphate, lactic acid dehydrogenase (LDH), uric acid and albumin.
- serum immunoglobulin levels (IgG, IgM, IgA)

- coagulation

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

For categorical variables, 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.

6.3. Death

A summary of deaths will be displayed for the safety analysis set. Frequencies for the following parameters will be included in the summary table:

- Number of subjects who died
- Cause of death
- If the primary cause of death is an AE, relationship to study agent (yes/no)

A summary of the number of deaths since first administration of study agent until 30 days after last study agent administration will also be provided, along with the primary cause of death. A listing of subjects who died will be provided.

Deaths due to COVID-19 will be listed separately.

6.4. Vital Signs and Physical Examination Findings

Descriptive statistics of weight, temperature, heart rate, respiratory rate, and blood pressure (systolic and diastolic) values and changes from baseline will be summarized at each scheduled time point.

6.5. Eye-related symptom assessment

Proportion of subjects with abnormal eye-related symptoms will be calculated at each scheduled time point. A data listing will be provided for abnormal ophthalmologic exam findings, including subject ID, visit, assessment date, ophthalmologic exam, and description of abnormal findings.

6.6. Other Safety Parameters

Eastern Cooperative Oncology Group (ECOG) status will be summarized by each scheduled timepoint.

In addition, a data listing by subjects will be provided.

7. PHARMACOKINETICS

Pharmacokinetic evaluable analysis set will be used for PK analyses. The individual plasma concentration data of ibrutinib and its metabolite PCI-45227 will be listed and graphically displayed (linear scale and/or semi-log 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 will be graphically displayed if possible. Concentration data below the lowest quantifiable concentration will be treated as zero in the summary statistics.

Subgroup analysis by ibrutinib dose and concomitant CYP3A inhibitors may be performed on the individual pre-dose plasma concentration at Week 5 Day 1 and Week 9 Day 1 of ibrutinib and PCI-45227. Necessity of subgroup analysis will be determined based on the actual number of subjects who received concomitant CYP3A inhibitors and/or dose reduction till the pre-dose of Week 9 Day 1. Summary tables and visual comparisons may be provided to present the summary statistics derived for each subgroup, if possible. The visual comparisons graphical presentation may also be performed for dose-normalized pre-dose plasma concentration of ibrutinib at Week 5 Day 1 and Week 9 Day 1 regardless of ibrutinib dose.

Additional analyses may be performed as deemed necessary.

Based on the individual plasma concentration-time data, using the actual dose taken and the actual sampling times, PK parameters and exposure information of ibrutinib may be derived using population PK modelling, if it is deemed appropriate and if data allow.

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.

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.

REFERENCES

1. Owen RG, Kyle RA, Stone MJ et al. Response assessment in Waldenström's macroglobulinemia: update from the VIth International Workshop. Br. J. Haematol. 160(2), 171 – 176 (2013).
2. Clinical Practice Guidelines in Oncology: Waldenström's macroglobulinemia/lymphoplasmacytic lymphoma version 1.2019. www.nccn.org/professionals/physician gls/pdf /waldenstroms.pdf