Johnson & Johnson Private Limited

Statistical Analysis Plan

A prospective, multicenter, open label single arm Phase IV clinical trial to assess safety of ImbruvicaTM (Ibrutinib capsules 140 mg) in Indian patients with chronic lymphocytic leukemia or mantle cell lymphoma who have received at least one prior therapy or chronic lymphocytic leukemia with 17p deletion

Protocol 54179060LYM4005 ; Phase IV

JNJ-54179060 Imbruvica (Ibrutinib capsule 140mg)

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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

Version	Effective Date	Changes	Rationale
1.0	23-Jun-2022	Not Applicable	Initial release
2.0	06-Feb-2023	1. General analysis definition summary section 2 has been updated to add (Table 1A) for visit windows. 2. Clinical Laboratory Tests (section 6.2) has been updated for sensitivity analysis 3. Vital Sign and Physical Examination (section 6.3) has been updated to add Table 4 for Normal Ranges for Vital Signs 4. Progression-Free Survival (section 5.1.4) has been updated to add PFS analysis	1.The visit window is applied in order to have the new set of analysis visits based on the T&E schedule available in the protocol. 2.Clinical Laboratory data was not captured prior to dose administration, so baseline definition is re-considered, used for sensitivity analysis (section 6.2). 3.Normal Ranges for Vital Signs can provide sufficient information to describe the Abnormality results. 4.PFS interpretation can provide sufficient information to describe the assessment criteria

ABBREVIATIONS

ADA	anti-drug antibody
ADR	adverse Drug Reaction
AE	adverse event
ATC	anatomic and therapeutic Class
BMI	body mass index
BSA	body surface area
BTK	Bruton's Tyrosine Kinase
CI	confidence interval
CL	total systemic clearance
CR	complete response
CRF	case report form
CSR	Clinical Study Report
dell 17p	deletions in the short arm of chromosome 17
DMC	Data Monitoring Committee
ECOG	Eastern Cooperative Oncology Group
ECG	electrocardiogram
eCRF	electronic case report form
eDC	electronic data capture
EORTC QLQ C-30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaires Core 30
EOT	End-Of-Treatment
FDA	Food and Drug Administration
FACIT	Functional Assessment of Chronic Illness Therapy
GCP	Good Clinical Practice
ICH	International Conference on Harmonization
ICF	Informed Consent Form/Document
IRB	Institutional Review Board
IWCLL	International Workshop on Chronic Lymphocytic Leukaemia
MCL	Mantle Cell Lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
PD	preferred term
PI	principal investigator
PR	partial response
PRO	Patient-Reported Outcome
PT	preferred term
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SD	stable disease
SMQsSLL	Standardised MedDRA queries Small Lymphocytic Lymphoma
SOC	system organ class
TEAE	treatment-emergent adverse event
US NCI	United States National Cancer Institute
WHO	World Health Organization
WHO-DD	World Health Organization Drug Dictionary

1. INTRODUCTION

Ibrutinib (PCI-32765; JNJ-54179060) is a first in class potent, orally administered, covalently binding small molecule inhibitor of Bruton's tyrosine kinase (BTK) currently under development for the treatment of B-cell malignancies.

This study is designed to assess the safety of Imbruvica™ (ibrutinib capsule 140 mg) prescribed as per locally approved prescribing information in Indian patients of chronic lymphocytic leukemia (CLL) or mantle cell lymphoma (MCL) who have received at least one prior therapy or CLL with 17p deletion.

This statistical analysis plan (SAP) for the 54179060LYM4005 describes the statistical analysis for subject information, safety data and clinical response.

1.1. Trial Objectives

Primary Objective

The primary objective of this study is to evaluate the safety of Imbruvica™ (ibrutinib capsule 140 mg) under actual conditions of use, and to understand the Incidence of adverse events (AEs) (Serious and Non-serious AEs).

Exploratory Objectives

To analyse the following outcomes with ibrutinib:

- Baseline patient and disease characteristics
- Response assessment and progression criteria as per International Workshop on Chronic Lymphocytic Leukaemia (IWCLL) criteria for CLL and revised response criteria for malignant lymphoma for MCL.
- Change in patient reported outcomes as measured by
  - Quality of Life by EORTC QLQ C-30 instrument (European Organization for Research and Treatment of Cancer Quality of Life Questionnaires Core 30)
  - Fatigue by FACIT Fatigue instrument (Functional Assessment of Chronic Illness Therapy Fatigue)

1.2. Trial Design

This is a prospective open label, single arm, multicenter, phase IV interventional study to describe the safety of Imbruvica™ in Indian subjects. Approximately, 75 subjects selected by investigators and determined to be eligible for ibrutinib treatment as per protocol eligibility criteria will be enrolled in the study.

The recommended dose of Imbruvica™ as per the locally approved prescribing information is 420 mg (three 140 mg capsules) as a single daily dose for CLL and 560 mg (four 140 mg capsules) as a single daily dose for MCL.

Screening cum Enrolment Visit (Day 1)

Prior to data collection, all subjects [and/or their legally acceptable representative where applicable] must sign an informed consent form (ICF) allowing data collection and source data verification in accordance with local regulations. Data collected at this visit may include but not limited to demographics, medical history, disease related history, concomitant medications, patient-reported outcomes (PROs), laboratory investigations, etc.

Treatment Period (Visits 1 to 6 and Visit 7)

Enrolled subjects will be followed up to 12 months from the treatment initiation. During the study period, data will be collected at monthly intervals for the first 6 months, (monthly visit ± 7 days; Visits 1 to 6). Subsequent visit would be at 9 months ± 7 days [Visit 7].

End-of-Treatment (EOT) (Visit 8)

The End-of-Treatment (EOT) visit will be conducted after the completion of 12-months Imbruvica™ treatment (at Visit 8) or on the day at which the patient discontinued the Imbruvica™ treatment or study.

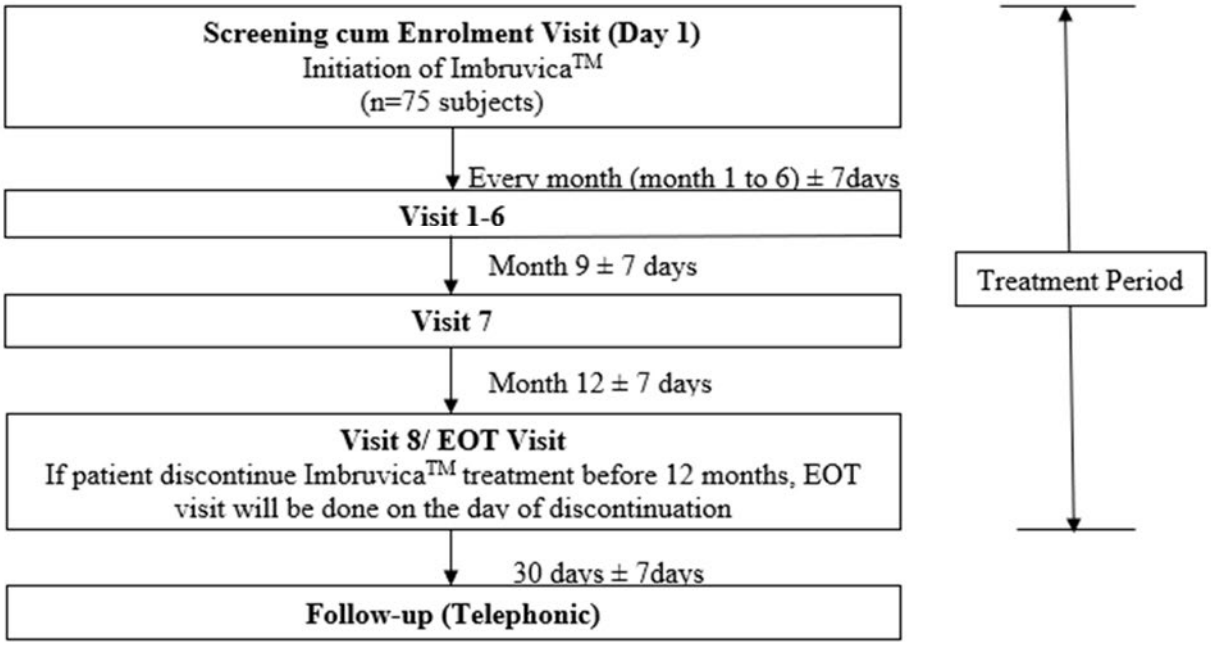
The end of the treatment will be the End of Treatment visit within the study for the last participating patient.

Follow up period (End of Study)

A telephonic follow-up will be conducted 30 days after the EOT Visit.

The observation period including the Enrolment Visit and telephonic Follow-up will be up to a maximum duration of 13 months for each patient.

Schematic Overview of the study



The overall duration of the study, including recruitment [and/or follow up], is expected to be 36 months.

1.3. Statistical Hypotheses for Trial Objectives

No formal hypothesis testing will be conducted. Data will be summarized using descriptive statistics. Continuous variables will be summarized using the number of observations, mean, SD, median, and range as appropriate. Categorical values will be summarized using the number of observations and percentages as appropriate. Exploratory endpoints will be summarized using descriptive statistics.

1.4. Sample Size Justification

The primary objective of this study is to estimate the incidence of AEs in Indian subjects under actual conditions of use of Imbruvica™. A sample size of 75 subjects is as per the recommendations of Subject Expert Committee (Oncology & Hematology) made in its 70th meeting held on 23rd May 2018 at Central Drugs Standard Control Organization HQ, New Delhi communicated vide F.N. 12-10/2017-DC (Pt-Johnson-snd).

1.5. Randomization and Blinding

Randomization and blinding will not be applicable for this study as this is a single arm, open label study.

Participating sites will be encouraged to enroll subjects in a consecutive manner when subjects come for their regular consultation to minimize bias in patient selection.

2. GENERAL ANALYSIS DEFINITIONS

The below mentioned general principles will be followed throughout the study:

- The change from baseline is defined as the post-baseline value minus the baseline value. Definition of baseline is provided in section 2.3.
- Descriptive statistics will include number of non-missing subject (n), mean, median, standard deviation (SD), minimum and maximum values for continuous variables, and for categorical variables the frequencies and percentages of subjects will be presented.
- For continuous data, mean and median will be rounded to 1 decimal place more than original data, SD will be rounded to 2 decimal places more than original data and minimum and maximum will be displayed with the same precision as the original data.
- For categorical data, percentages will be rounded to 1 decimal place.
- If a count is 0, the percentage (0%) should not be displayed. The 0 count will be displayed, but the corresponding percentage should be omitted.
- All study data will be included in study data listings. In general, all data will be listed by time point within subject.
- In general, missing data will not be imputed.
- SAS® version 9.4 will be used for all analyses.
- Visit Windows for PRO analysis:

To allow for variation in scheduling, the following set of visit windows will be used to assign evaluations to a most appropriate visit for analysis (Avisit).

Table 1A:

Visit	Avisit	Start Day	Target Day	End Day
SCR/Enrollment visit/Month 1	Screening	-	1	1
Visit 1/ Month 2 (end of month 1)	Month 1	2	30	37
Visit 2/Month 3 (end of month 2)	Month 2	38	60	67
Visit 3/Month 4 (end of month 3)	Month 3	68	90	97
Visit 4/ Month 5 (end of month 4)	Month 4	98	120	127
Visit 5/ Month 6 (end of month 5)	Month 5	128	150	157
Visit 6/ Month 7 (end of month 6)	Month 6	158	180	187
Visit 7/ Month 10 (end of month 9)	Month 9	188	270	277
Visit 8 (end of month 12/End of Treatment)	Month 12	278	360	367

2.1. Analysis Sets

2.1.1. All Enrolled Analysis Set

All enrolled analysis set includes all subjects who had signed the informed consent form (ICF) and were enrolled in the study.

2.1.2. Safety Analysis Set

The safety analysis set includes all subjects who had signed the ICF and received at least one dose of Imbruvica™.

2.1.3. Efficacy Analysis Set

The efficacy analysis set will include all subjects who have taken at least 1 dose of study treatment and have both baseline and at least 1 post-baseline efficacy assessment.

2.2. Study Day and Relative Day

Study Day 1 or Day 1 refers to the start of the first study agent 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 Study 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'.

2.3. Baseline and Endpoint

Baseline is defined as the last non-missing observation on or prior to the start of the first study agent administration.

Primary Endpoint

- The number and type of TEAEs reported by the investigator or the patient.

Exploratory Endpoints

- Proportion of subjects experiencing clinical response as per assessment criteria defined in section 9.1 of the protocol.
- Change from baseline in patient-reported outcomes as per EORTC QLQ C-30 and FACIT Fatigue

3. INTERIM ANALYSIS AND DATA MONITORING COMMITTEE REVIEW

For the study no interim analysis and data monitoring committee (DMC) review is planned.

4. SUBJECT INFORMATION

4.1. Demographics and Baseline Characteristics

Table 1 presents a list of the demographic variables that will be summarized for the safety analysis set.

Table 1: Demographic Variables

Continuous Variables:	**Summary Type**
Age (years)	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum]).
Weight (kg)	
Categorical Variables	
Sex (male, female, unknown, undifferentiated)	Frequency distribution with the number and percentage of subjects in each category.
Race (INDIAN)	

Table 2: Baseline Characteristics

Baseline characteristics	**Summary Type**
Type of disease Staging Number of prior therapies ECOG status at baseline	Frequency distribution with the number and percentage of subjects in each category.
Number of years of diagnosis EORTC-QLQ-C30 at baseline FACIT Fatigue	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum]

4.2. Disposition Information

Number of enrolled subjects and screen failures will be summarized for all enrolled analysis set. The summary table and listing for treatment disposition and study disposition will be presented based on safety analysis set.

The summary for the treatment disposition will be as follows:

- Number of subjects receiving study agent
- Number of subjects who completed the study agent
- Number of subjects discontinued the study agent
- Reasons for discontinuation of study agent

The summary for the study disposition will be as follows:

- Number of subjects receiving study agent
- Number of subjects completed the study
- Number of subjects discontinued from the study
- Reasons for study discontinuation

A listing of subjects will be provided along with the dates, study days and reason for discontinuation/ termination for the following categories:

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

4.3. Treatment Compliance

Study drug compliance with actual amount taken/expected amount taken X 100% and for categories <80%, 80-<120%, ≥120% will be summarized.

4.4. Extent of Exposure

Summary for the total amount of study drug (Imbruvica™) received (mg), total treatment duration (month), total amount of study drug prescribed (mg), and the average daily dose (mg/day) will be presented. The average daily dose is calculated as (total amount of study drug received) / treatment duration.

A listing of subject receiving study agent (Imbruvica™) along with the start/stop dates, dose amount, frequency, indication and study day will be presented.

Additionally, if dosage reduction/adjustment of Imbruvica™ is needed, the number of percentages of subjects will be summarized and then date and reason for dose reductions/adjustment will be listed.

4.5. Protocol Deviations

Listing of subjects with major protocol deviations will be provided.

Subjects with major and minor protocol deviations related to Covid-19 (if any) will be listed separately.

A listing of subjects with inclusion/exclusion deviation will be listed, if applicable.

Note If there are a certain number of patients with COVID-19 infection and/or death due to COVID infection during the study, the impact of COVID-19 needs to be assessed. Based on the impact assessments, more listings and summary tables (regarding prior and concomitant, AE, efficacy and etc..) may be added to the analyses.

4.6. Prior and Concomitant Medications

Prior and Concomitant medications will be coded using the latest World Health Organization Drug Dictionary (WHO-DD). Prior medications are defined as any therapy used before the day of first dose (partial or complete) of 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.

The data on prior and concomitant medications will be listed separately for each subject.

4.7. Medical History

Medical History will be summarized and listed for all subjects on all enrolled analysis set.

5. EFFICACY/EXPLORATORY

5.1. Exploratory Endpoints

5.1.1. EORTC QLQ C-30

European Organization for Research and Treatment of Cancer Quality of Life Questionnaires Core 30.

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

5.1.2. FACIT Fatigue

Functional Assessment of Chronic Illness Therapy-Fatigue

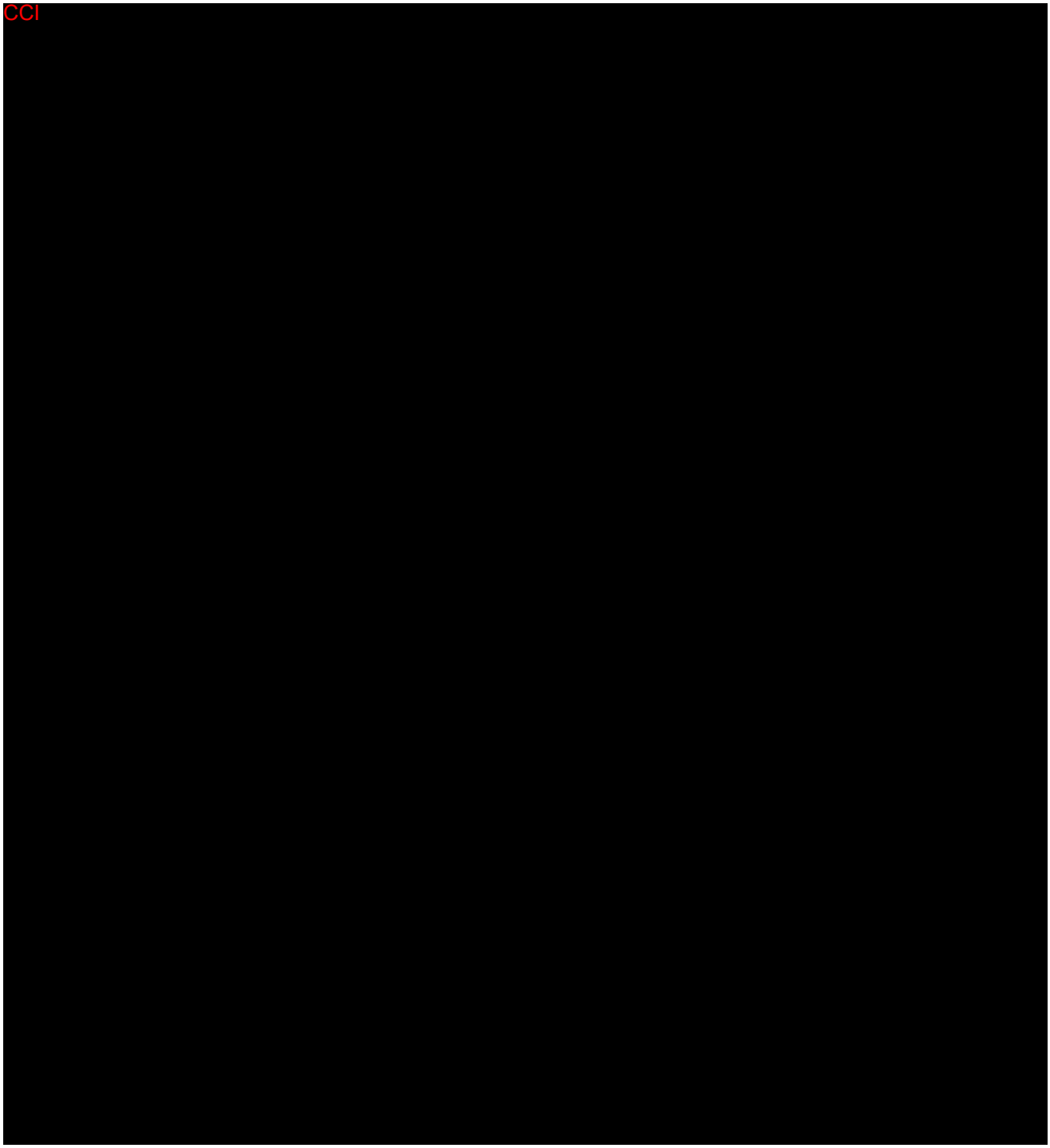
The PRO questionnaires will be collected preferably at the beginning of the clinic visits prior to any procedures or physician interactions

FACIT Fatigue is an instrument for use as a measure of the effect of fatigue in patients with cancer and other chronic diseases. Responses to the 13-item FACIT Fatigue Scale are reported on a 5-point categorical response scale ranging from 0 (not at all) to 4 (very much). Below is the list of items for FACIT-fatigue:

CCI

[redacted]

Figure 1



5.1.3. Proportion of subjects experiencing clinical response as per assessment criteria

Following are the response categories to be assessed:

- Complete Response (CR)
- Partial Response (PR)

- Stable Disease (SD)
- Disease Progressive (PD)

Analysis: The number and percentage of subjects will be provided in the following response categories: CR, PR, SD, PD. Data for response assessment will be listed individually for each subject at each visit for efficacy analysis set. The proportion of subjects who achieved the best response of (CR+PR) and its 95% confidence interval (CI) will be analyzed on efficacy analysis set.

5.1.4. Progression-Free Survival

Progression-Free Survival (PFS) is defined as the duration from the date of first dose of study drug to either progressive disease the IWCLL criteria or death, whichever occurs first. For subjects who have not progressed and are alive, data will be censored at the Visit 8, or last visit date. The Kaplan-Meier method will be used for descriptive summaries. Median PFS and its 95% CI will be provided. The PFS rates with 95% CI at selected landmark points (6 months and 12 months) will be calculated. PFS will be analyzed on both safety and efficacy analysis set.

6. SAFETY

All safety analyses will be based on the safety analysis set 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 case report form (CRF) by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Any AE occurring at or after the initial administration of study agent through the day of last dose is considered to be treatment emergent. 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 percentage of subjects who experience at least 1 occurrence of the given event will be summarized by treatment group.

Summary tables will be provided for:

- Overall summary of TEAEs
- TEAEs by SOC and PT

- TEAEs by SOC, PT, and severity (Mild, Moderate and Severe)
- TEAEs by SOC, PT, and NCI-CTCAE toxicity grade (for non-hematological AEs (using NCI-CTCAE Version 4)) TEAEs by SOC, PT, and IWCLL toxicity grade (for hematologic AEs (using IWCLL 2008 criteria))
- TEAEs by SOC, PT, and relationship to study agent (Not Related, Doubtful, Possible, Probable, Very Likely or Related [possible, probably, Very Likely] and Non-related)
- Serious TEAEs by SOC and PT
- Treatment related TEAEs by SOC, PT, and toxicity grade >= 3
- Treatment related serious TEAEs by SOC and PT
- TEAEs leading to discontinuation of study agent by SOC and PT
- AEs leading to death by SOC and PT

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

- Any TEAEs
- Serious TEAEs (SAEs)
- Severe TEAEs
- Treatment related TEAEs
- TEAEs leading to discontinuation of study agent
- AEs leading to Death

6.2. Clinical Laboratory Tests

The following summary tables will be presented by type of laboratory test:

- Descriptive statistics will be calculated for each laboratory analyte (Hematology and Coagulation) for observed values at each scheduled time point.
- Parameters with predefined National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE, Version 4) toxicity grades at each scheduled time point of measurement
- The number and percentage of subjects with NCI-CTCAE grade >= 3 (markedly abnormal) for the parameters with predefined NCI-CTCAE toxicity grades at each scheduled time point of measurement
- Subjects with abnormal laboratory values at all measured time point.
- Subjects with any markedly abnormal laboratory results
- Normal reference ranges.

Since there is no conventional baseline visit, the values and abnormalities will be summarized by visit without change from baseline analysis. But the sensitivity analysis will be performed with baseline defined as Visit 1.

- Descriptive statistics will be calculated for each laboratory analyte (Hematology and Coagulation) at baseline and for observed values and changes from baseline at each scheduled time point.
- Shift tables (cross-tabulations) summarizing the shift in laboratory values from baseline to the worst post baseline measurement experienced by the subject during the study with respect to NCI-CTCAE toxicity grades
- Shift tables (cross-tabulations) summarizing the shift in laboratory values for non-graded parameters from baseline to each scheduled time point of measurement with respect to abnormality criteria (low, normal, high).
- For all participants, a listing to support the sensitivity analysis table will be provided which will include clinical laboratory test results and change from baseline at all measured time points.

6.3. Vital Signs and Physical Examination

- Descriptive statistics of temperature, pulse/heart rate, respiratory rate, mean arterial pressure and blood pressure (systolic and diastolic values) and changes from baseline will be summarized at each scheduled time point
- The percentage of subjects with values beyond clinically important limits will be summarized.
- Listing of vital sign measurements and the change from baseline will be presented for all participants.
- A listing of abnormal vital signs will be presented, including unscheduled visits.

Table 4: Normal Ranges for Vital Signs

Parameter	Range	Unit
Body temperature	36.1 – 37.2	C
Pulse rate	60 – 100	beats/min
Systolic Blood Pressure	90 – 120	mmHg
Diastolic Blood Pressure	60 – 80	mmHg
Mean Arterial Pressure	70 - 100	mmHg
Respiratory Rate	12 – 20	breaths/min

Physical examination findings will be listed.

6.4. ECOG Performance Status

Subjects will be listed with its performance status at all the schedule timepoints. Counts and percentages of ECOG will be presented at scheduled visits.

7. REFERENCES

1. https://www.eortc.org/app/uploads/sites/2/2018/02/SCmanual.pdf
2. FACIT-F_INDICE.pdf (ser.es)