Statistical Analysis Plan LOXO-BTK-20020 (J2N-OX-JZNN) Version 3.0

Study of LOXO-305 Versus Investigator's Choice (IdelaR or BR) in Patients With Previously Treated Chronic Lymphocytic Leukemia (CLL)/ Small Lymphocytic Lymphoma (SLL) (BRUIN CLL-321)

NCT04666038

Approval Date: 06-Sep-2023

STATISTICAL ANALYSIS PLAN FOR CLINICAL STUDY LOXO-BTK-20020

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Protocol Number: LOXO-BTK-20020 (J2N-OX-JZNN)

Protocol Title: A Phase 3 Open-Label, Randomized Study of LOXO-305 versus Investigator's Choice of Idelalisib plus Rituximab or Bendamustine plus Rituximab in BTK Inhibitor Pretreated Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (BRUIN CLL-321)

Compound Number: Pirtobrutinib (LOXO-305, LY3527727)

Current Version 3.0: 06 SEPTEMBER 2023

STATISTICAL ANALYSIS PLAN
PROTOCOL LOXO-BTK-20020
SIGNATURE PAGE

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LIST OF ABBREVIATIONS

Term	Definition
ADI	actual dose intensity
AE	adverse event
AEPCS	adverse event of potential clinical significance
AESI	adverse event of special interest
BID	twice a day
BOR	best overall response
BR	bendamustine with rituximab
BTK	Bruton's tyrosine kinase
CI	confidence interval
CLL/SLL	chronic lymphocytic leukemia/small lymphocytic lymphoma
CMH	Cochran-Mantel-Haenszel
CONSORT	Consolidated Standards of Reporting Trials
CR	complete response
CRF	case report form
CRi	complete response with incomplete bone marrow recovery
CSR	clinical study report
CTCAE	Common Terminology Criteria in Adverse Events
CTR	clinical trial registry
DMC	Data Monitoring Committee
DoR	duration of response
ECG	electrocardiograms
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EFS	event-free survival
FISH	fluorescence in situ hybridization
HR	hazard ratio
IdelaR	idelalisib with rituximab
IPD	important protocol deviations
IRC	Independent Review Committee
ITT	intention to treat
IV	intravenous(ly)
iwCLL	International Workshop on Chronic Lymphocytic Leukemia
IXRS	interactive voice/web response system
KM	Kaplan-Meier
LFT	liver function test
MedDRA	Medical Dictionary for Regulatory Activities
NCI-CTCAE	National Cancer Institute - Common Terminology Criteria for Adverse Events
NED	no evidence of disease

Term	Definition
nPR	nodular partial response
ORR	overall response rate
OS	overall survival
PD	progressive disease
PDI	planned dose intensity
PFS	progression-free survival
PK	pharmacokinetics
PO	by mouth
PR	partial response
PR-L	partial response with lymphocytosis
PRO	patient-reported outcome
PT	preferred term
QD	once daily
RBC	red blood cell
RDI	relative dose intensity
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SOC	system organ class
TEAE	treatment-emergent adverse event
TOT	time on treatment
TTF	time to treatment failure
TTNT	time to next treatment
TTW	time to worsening
UNK	unknown

VERSION HISTORY

This SAP is based on version 6.0 of the protocol for Study LOXO-BTK-20020 dated 15 February 2023.

SAP Version	Approval Date	Change	Rationale
1.0	11 Jun 2021	Not Applicable	Original version
2.0	19 Jun 2023	Change the study drug name from LOXO-305 to pirtobrutinib	Align with the current version of the study protocol
		Remove time to treatment failure	Align with the current version of the study protocol
		Add additional sensitivity analysis to IRC-PFS, OS	Additional sensitivity analysis to evaluate impact of censoring rule and crossover data
		Add subgroup analysis for OS	Add subgroup analysis to better characterize key secondary efficacy endpoint OS
		Update subgroup analysis for Race/Ethnicity	Update to incorporate diversity, equity, and inclusion plan
3.0	06 Sep 2023	Add descriptive interim analysis for OS	Allow data maturity in OS with extended follow-up
		Update in Handling of Missing Data	Align with eCRF data collection and data standard
		Clarification language on sensitivity analysis regarding IPD for IRC-PFS	Align with IPD review process
		Clarification language on subgroup analysis	Provide analysis method for small sample size in subgroups
		Add TTNT censoring rule	Align with other efficacy endpoints
		Miscellaneous revisions	Align with EDC data capture, data standard; minor corrections

1.0 INTRODUCTION

The purpose of this SAP is to provide details of the statistical analyses for Study LOXO-BTK-20020 (also referred to as BRUIN CLL-321), which is entitled "A Phase 3 Open-Label, Randomized Study of LOXO-305 versus Investigator Choice of Idelalisib plus Rituximab or Bendamustine plus Rituximab in BTK Inhibitor Pretreated Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (BRUIN CLL-321)."

There are no changes to the analyses described in the protocol.

1.1 Objectives, Endpoints, and Estimands

1.1.1 Objective and Endpoints

Objectives	Endpoints
Primary	
Evaluate progression-free survival (PFS) of pirtobrutinib as monotherapy (Arm A) to Investigator's choice of idelalisib plus rituximab (IdelaR) or bendamustine plus rituximab (BR) (Arm B).	Assessed by independent review committee (IRC) PFS per International Workshop on Chronic Lymphocytic Leukemia (iwCLL) 2018 criteria
Secondary	
Evaluate the effectiveness of Arm A compared to Arm B based on overall response rate (ORR) and time-to-event(s) outcomes.	Assessed by Investigator: PFS per iwCLL 2018 criteria Overall survival (OS) Time to next treatment (TTNT), defined as time from the date of randomization to the date of the next systemic anticancer therapy for CLL/SLL or death, whichever occurs first Event-free survival (EFS) defined as the time from date of randomization to the date of progressive disease (PD) or start of new treatment for CLL/SLL or discontinuation from study treatment due to toxicity or death due to any cause, whichever occurs first Assessed by Investigator and IRC: ORR Duration of response (DoR)
Evaluate the safety and tolerability of each treatment arm.	Including, but not limited to, serious adverse events (SAEs), adverse events (AEs), deaths, and clinical laboratory abnormalities per National Cancer Institute Common Terminology Criteria in Adverse Events v5.0 (NCI-CTCAE v5.0).
Evaluate the effectiveness of Arm A compared to Arm B based on patient-reported outcomes (PRO).	Patient-reported outcomes of: Time to worsening (TTW) of CLL/SLL-related symptoms TTW of physical functioning

Objectives	Endpoints
Tertiary/Exploratory	
CCI	

The estimands are described below following the ICH E9 (R1) addendum (European Medicines Agency 2020).

1.1.2 Primary Estimand

The primary research question is: What is the difference in PFS between pirtobrutinib and Investigator's choice of IdelaR or BR as treatment for patients with CLL/SLL who have been pretreated with covalent BTK inhibitor?

The estimand for the primary objective is described by the following attributes:

- **Population:** adult patients with CLL/SLL who have been pretreated with covalent BTK inhibitor and randomized to study intervention (Primary Analysis population). Further details can be found in Protocol Section 5, Study Population.
- **Endpoint:** IRC-assessed PFS in the Primary Analysis populations, which is defined as the time from randomization until the earlier occurrence of documented PD by IRC or death without documented PD.
- **Treatment condition:** the randomized study intervention (pirtobrutinib or IdelaR or BR) will be administered in 28-day cycles until meeting any protocol-defined reason for treatment discontinuation or completing the assigned treatment. Further details on study interventions including interventions, concomitant therapy, and dose modification can be found in Protocol Section 6, Study Intervention.
- **Intercurrent-event strategies:**
  - Subsequent anticancer therapy for CLL/SLL prior to PD or death without PD is handled with on treatment strategy.
  - Extended time without adequate disease assessment (i.e., 2 or more consecutively missed disease assessment visits) prior to PD or death without PD is handled with on treatment strategy.
  - Study intervention discontinuation prior to PD or death without PD is handled with treatment policy strategy.

- **Population-level summary measure:** HR of PFS comparing pirtobrutinib vs IdelaR or BR estimated using a stratified Cox regression model (Cox 1972)
- **Rationale for estimand:** The interest lies in the relative treatment effect without the confounding effect of the subsequent anticancer therapy for CLL/SLL or extended time without adequate assessment.

A subsequent anticancer therapy for CLL/SLL taken prior to PD or death without progression will confound the treatment effect of pirtobrutinib in terms of PFS. If the subsequent anticancer therapy is taken, future disease recurrence/progression status is not needed. The participant will be censored and only the time prior to the initiation of the subsequent anticancer therapy will be considered in analysis.

PD or death without progression observed after an extended time without adequate disease assessment may have occurred much earlier but is not reported because the scheduled assessment was not done. This inadequate observation may introduce bias to PFS estimates. If extended time without adequate assessment occurs, the participant will be censored and only the time up to the last adequate tumor assessment will be considered in analysis.

Study intervention discontinuation due to reasons other than PD or death without progression is handled with treatment policy as it reflects clinical practice. Time from randomization until disease progression, or death without PD, regardless of study intervention discontinuation, will be considered in analysis.

1.1.3 Secondary Estimands

1.1.3.1 Overall Survival

A secondary research question is: What is the difference in OS between pirtobrutinib and Investigator's choice of IdelaR or BR as treatment for patients with CLL/SLL and pretreated with covalent BTK inhibitor?

The estimands for the secondary objective are described by the following attributes:

- **Population:** adult patients with CLL/SLL and pretreated with covalent BTK inhibitor and randomized to study intervention (Primary Analysis population during the entire study including the crossover period). Further details can be found in Protocol Section 5, Study Population.
- **Endpoint:** OS, which is defined as the time from randomization until death from any cause.
- **Treatment condition:** the randomized study intervention (pirtobrutinib versus IdelaR or BR) will be administered in 28-day cycles until any protocol-defined reason is met for study discontinuation or the assigned treatment is completed. Further details on study interventions, including interventions, concomitant therapy, and dose modification, can be found in Protocol Section 6, Study Intervention.

- **Intercurrent-event strategies:**
  - Study intervention discontinuation prior to death is handled with treatment policy strategy.
  - Subsequent anticancer therapy for CLL/SLL (including pirtobrutinib for crossover participants) prior to death is handled with treatment policy strategy.
- **Population-level summary measure:** Hazard ratio of OS in pirtobrutinib vs IdelaR or BR estimated using a stratified Cox regression model (Cox 1972).
- **Rationale for estimand:** The interest lies in whether there is treatment benefit in OS where patients are treated with pirtobrutinib after prior covalent BTK inhibitor treatment and with other anticancer therapies after PD or death without PD. Study intervention discontinuation due to reasons other than death and subsequent anticancer therapy for CLL/SLL taken prior to death are handled with treatment policy as it reflects clinical practice for patients.

1.2 Study Design

LOXO-BTK-20020 (BRUIN CLL-321) is a Phase 3, global, multicenter, randomized (1:1), open-label study comparing pirtobrutinib as continuous monotherapy (Arm A) to Investigator's choice of either idelalisib plus rituximab (IdelaR) or bendamustine plus rituximab (BR) (Arm B) in CLL/SLL patients who have been treated with a covalent BTK inhibitor, approved (ibrutinib or acalabrutinib) or investigational.

BRUIN CLL-321 will enroll adult CLL/SLL patients with an indication for treatment as defined by iwCLL 2018 criteria (Hallek et al. 2018). During Screening, Investigator's choice therapy (IdelaR or BR) must be selected by the Investigator prior to randomization for each patient. Patients who have been treated previously with IdelaR or BR and had either documented PD as determined by the Investigator or could not tolerate the regimen should not be retreated with same regimen. Eligible patients will be randomized 1:1 to either Arm A or Arm B based on the following stratification factors:

- Deletion 17p presence (yes, no)
- Receipt of prior venetoclax treatment (yes, no)

After confirmation of eligibility, approximately 250 patients will be randomly assigned in a 1:1 ratio to

- Arm A: pirtobrutinib (200 mg PO QD) every 28 days, continuously, or
- Arm B: Investigator's choice of the following therapies:
  - idelalisib (150 mg PO BID, every 28 days continuously) plus rituximab (375 mg/m^2 on C1D1 for the first 28-day cycle and then 500 mg/m^2 every 2 weeks for 4 doses (C1D15, C2D1, C2D15, C3D1) and then every 4 weeks for 3 doses (C4D1, C5D1, C6D1) for a total of 8 doses)

- bendamustine (6 cycles at 70 mg/m^2 IV on Days 1 and 2 of each cycle) plus rituximab (375 mg/m^2 Day 1 of the first cycle and 500 mg/m^2 Day 1 of Cycles 2 to 6)

Study treatment will be given until PD, unacceptable toxicity, withdrawal of consent, death or initiation of a new anticancer therapy, or treatment completion occurs. Patients randomly assigned to Arm B will be allowed to cross over to Arm A upon confirmation of PD by IRC and if they meet the eligibility criteria for crossover (Protocol Section 5.3). Patients who have PD per the Investigator's assessment but not IRC assessment are not eligible for crossover until they meet IRC PD criteria.

A detailed description of the study design is contained in the protocol.

2.0 STATISTICAL HYPOTHESES

2.1 Primary Hypothesis

Treatment with pirtobrutinib as continuous monotherapy will provide superior PFS (assessed by IRC) over treatment with Investigator's choice of idelalisib plus rituximab or bendamustine plus rituximab in patients with covalent BTK inhibitor pretreated CLL/SLL.

2.2 Multiplicity Adjustment

The statistical comparisons for the primary efficacy endpoint and the key secondary endpoint will be carried out in the hierarchical order:

- IRC-assessed PFS, then
- OS

To be specific, only if the test of IRC-assessed PFS is statistically significant will OS be tested inferentially for statistical significance. Since a hierarchical group sequential gate-keeping strategy (Glimm et al. 2010) is used, each hypothesis will be tested at CCI [redacted] (see CCI [redacted] details for each endpoint over interim and final analyses in Section 4.8), and a family-wise type I error will be controlled at CCI [redacted]

3.0 ANALYSIS SETS

For purposes of analysis, the following populations are defined:

Population	Description
Entered	All participants who sign informed consent.
Intention to treat (ITT)	All randomized patients, even if a patient does not take the assigned treatment, does not receive the correct treatment, or otherwise does not follow the protocol. Patients will be analyzed according to the treatment arm they were assigned to regardless of what actual treatment they receive. Unless otherwise specified, all analyses using the ITT population will include data only prior to crossover for Arm B patients who crossed over to Arm A, except for OS related analyses.

Population	Description
Safety	All randomized patients who take at least 1 dose (including a partial dose) of study treatment. Analysis of safety data will be based on the actual treatment a patient received on the first study treatment administration, regardless of which treatment they were randomized to receive ("as treated"). Unless otherwise specified, all analyses using the Safety population will include data collected prior to crossover for Arm B patients who crossed over to Arm A.
Crossover	A subpopulation of patients included in the ITT population who were randomized to Arm B and crossed over to receive at least 1 dose of pirtobrutinib. The Crossover population will be used for selected safety analyses including data collected during crossover period starting from the date of first dose of pirtobrutinib, if deemed necessary.

4.0 STATISTICAL ANALYSES

4.1 General Considerations

Statistical analysis of this study will be the responsibility of Loxo Oncology, Inc. or its designee. All tests of treatment effects will be conducted at a two-sided alpha level of CCI, unless otherwise stated, and all CIs will be given at a CCI level, unless otherwise stated. Statistical analysis will be performed using SAS software (SAS, version 9.4 or higher).

Continuous variables will be summarized using descriptive statistics (i.e., number of patients, mean, median, standard deviation, Q1, Q3, minimum, and maximum). Categorical variables will be summarized by frequency and its corresponding percentage.

All efficacy (except OS analyses) and safety analyses will include data prior to crossover for Arm B patients who crossed over to Arm A (ITT and Safety populations, respectively). OS will be analyzed based on ITT population during the entire study, including the crossover period. The safety data during crossover period will be summarized and reported separately.

Any change to the data analysis methods described in the protocol will require an amendment only if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the clinical study report. Additional exploratory analyses of the data will be conducted as deemed appropriate.

4.1.1 Definitions

Definitions of efficacy, safety, and PRO analysis variables are listed in respective sections of the SAP. Other variables are listed below alphabetically:

- **Age (years):** (informed consent date - date of birth + 1) / 365.25; Birth month and day are imputed to be 01 July because only birth year is collected through eCRF.

- **Baseline Measurement:** unless otherwise specified, the last nonmissing measurement prior to the first dose of study treatment. Baseline measurement of radiographic imaging will use the last nonmissing measurement on or prior to date of randomization.
- **Crossover Period:** the crossover period is defined only for patients who were randomized to Arm B and crossed over to pirtobrutinib, and the crossover period is defined as time from date of first dose of crossover pirtobrutinib monotherapy to study discontinuation date.
- **Duration:** duration is calculated as:
  - Duration (days): (end date – start date + 1)
  - Duration (weeks): (end date – start date + 1) / 7
  - Duration (months): (end date – start date + 1) / 30.4375
    (days in months = (1/12) × average number of days in a year)
  - Duration (years): (end date – start date + 1) / 365.25
- **Duration of disease:** (randomization date – diagnosis of cancer date + 1)
- **Study Day (safety and tolerability analyses):**
  - If the assessment is done on or after the first dose day: assessment date – first dose date + 1
  - If the assessment is done prior to the first dose day: assessment date – first dose date
  - Date of first dose is defined as Study Day 1. Study date for Arm B patients will not include the crossover period.
- **Study Day (baseline and efficacy analyses):**
  - If the assessment is done on or after randomization: assessment date – randomization date + 1
  - If the assessment is done prior to randomization: assessment date – randomization date
  - Date of randomization is defined as Study Day 1. Study date for Arm B patients will not include the crossover period except OS related analyses.
- **Study Day for Crossover Period:**
  - Study day for crossover period is only defined for Arm B patients who crossed over to pirtobrutinib.
  - Study day is calculated as assessment date – date of first dose of pirtobrutinib + 1 day.
  - If the assessment is done prior to the first dose day, study day will be calculated as assessment date – first dose date.
  - Date of first dose is defined as Crossover Period Study Day 1.
- **Time to Event:** the event or censoring time (days) is calculated as date of event/censoring – randomization date + 1.

4.1.2 Handling of Dropouts or Missing Data

All analyses and descriptive summaries will be based on the observed data. Unless otherwise specified, missing data will not be imputed or "carried forward." Rules for handling dropouts or missing data are listed by type of analysis alphabetically.

- AE:
  - The missing day of onset of an AE will be set to:
    - First day of the month that the event occurred, if the onset yyyy-mm is after the yyyy-mm of first study treatment;
    - The day of the first study treatment, if the onset yyyy-mm is the same as yyyy-mm of the first study treatment; or
    - The date of informed consent or first day of the month that the event occurred, whichever is later, if the onset yyyy-mm is before the yyyy-mm of the first treatment, or if the onset yyyy-mm is the same as yyyy-mm of the first study treatment and AE resolution date is on or before the date of the first study treatment.
  - The missing day of resolution of an AE will be set to:
    - The last day of the month of the occurrence. If the patient died in the same month, then set the imputed date as the death date.
  - If the onset date of an AE is missing both the day and month, the onset date will be set to:
    - 01 January of the year of onset, if the onset year is after the year of the first study treatment;
    - The date of the first treatment, if the onset year is the same as the year of the first study treatment; or
    - The date of informed consent or 01 January of the year of onset, if the onset year is before the year of the first treatment, or if the onset year is the same as the year of the first study treatment and AE resolution date is on or before the date of the first study treatment.
  - If the resolution date of an AE is missing both the day and month, the date will be set to:
    - 31 December of the year of occurrence. If the patient died in the same year, then set the imputed date as the death date.
  - If the date is completely missing, then no imputation will be done and the event will be considered as treatment-emergent with unknown onset date, unless the end date rules out the possibility.
- Missing or partially missing start or end dates for medications will be imputed based on the conventions described in Section 6.3.
- Diagnosis date, the following conventions will be used for imputing partial dates:

  - If only the day of the month is missing, the 15th of the month will be used to replace the missing day.
  - If both the day and the month are missing, "01 Jul" will be used to replace the missing information.
- General rule for imputing other dates:
  - If only the day is missing, then assign Day 15 of the month, or the date of death if the patient died prior to 15th of the same month to the day.
  - If month is missing, then the date will be set to July 1st of the year, or the date of death if the patient died prior to July 1st of the same year.
- In all cases, after imputation, check if the imputed date is logically consistent with other relevant date variable(s) and make appropriate correction if necessary.
- Time-to-event analysis: all censored data will be accounted for using appropriate statistical methods.

4.2 Participant Dispositions

A detailed description of participant disposition will be provided according to the CONSORT publishing requirements, including a summary of the number and percentage of patients entered into the study, randomized in the study, and treated, as well as number and percentage of patients completing the study or discontinuing (overall and by reason for discontinuation).

Patient disposition for Crossover population will be summarized in a separate table.

4.2.1 Protocol Deviations

Protocol deviation categories are defined and managed by the study team during the protocol deviation reviews throughout the study before database lock. These definitions of protocol deviation categories and descriptions will be used during the course of the study. The final IPD list is used to produce the summary of IPD table and listing. In addition, this final IPD list will also be reviewed to identify those that could impact efficacy analysis and will be identified accordingly to support IRC-assessed PFS sensitivity analysis (Section 4.3.3).

4.3 Primary Endpoints Analysis

4.3.1 Definition of Endpoint(s)

The primary endpoint of PFS assessed by the IRC is defined as the time from randomization until the occurrence of documented disease progression by the IRC, per iwCLL 2018 criteria (Hallek et al. 2018; Cheson et al. 2012), or death from any cause in the absence of documented PD. Patients known to be alive and without PD will be censored at the time of the last adequate disease assessment.

The analysis of IRC-assessed PFS is event driven. The final analysis will be conducted when approximately CCI events assessed by IRC have been observed.

4.3.2 Main Analytical Approach

The IRC-assessed PFS will be compared between treatment arms using a stratified logrank test, stratified by the 2 randomization strata based on the IWRS data: del 17p presence (yes versus no) and receipt of prior venetoclax treatment (yes versus no). The corresponding HR between treatment arms will be estimated using a stratified Cox regression model (Cox 1972). PFS KM survival curves, medians, and PFS rates at various time points with 95% CI for each treatment arm will be estimated using the KM method (Kaplan and Meier 1958). The table in Section **Error! Reference source not found.** defines censoring rules to be applied to the IRC-assessed PFS main analysis.

4.3.3 Sensitivity Analyses

Several sensitivity analyses for the IRC-assessed PFS will be conducted as defined below:

- Repeat the primary analysis for IRC-assessed PFS using unstratified logrank test and an unstratified Cox regression model.
- Subjects with the use of any subsequent anticancer therapy prior to the first IRC confirmed PD or death due to any cause will not be censored at the last adequate assessment prior to the start date of the subsequent anticancer therapy.
- IRC-assessed PD or death after 2 or more consecutively missed visits will be included as a PFS event.
- Exclude patients with IPDs deemed to impact efficacy analysis

4.4 Secondary Efficacy Endpoints

4.4.1 Key Secondary Efficacy Endpoints

4.4.1.1 Overall Survival

4.4.1.1.1 Definition of Endpoint

OS is defined as the time from randomization until death from any cause. If the patient is alive or lost to follow-up at the time of data analysis, OS data will be censored on the last date the patient is known to be alive.

4.4.1.1.2 Main Analytical Approach

The analysis timepoint(s), gate-keeping strategy, and related alpha-spending scheme regarding OS analyses are described in Section 4.8. The analysis method of OS analysis will be similar to the main analysis for IRC-assessed PFS in Section 4.3.2. The table in Section 6.2.2 defines censoring rules to be applied to the OS analysis.

4.4.1.1.3 Sensitivity Analysis

A sensitivity analysis for OS will be conducted. Subjects who cross over from Arm B will be censored at the time of crossover.

4.4.2 Supportive Secondary Efficacy Endpoints

4.4.2.1 Overall Response Rate Assessed by IRC

ORR according to IRC-assessed BOR is defined as the number of patients who achieve a BOR of CR, CRi, nPR or PR at or before the initiation of subsequent anticancer therapy divided by the total number of patients randomized to each treatment arm. IRC-assessed best overall response is the best overall response recorded from the start of treatment until IRC-assessed PD, in the order of CR, CRi, nPR, PR, SD, nonPD, PD, NED, or UNK. Patients who do not have any post-baseline disease response assessments are considered nonresponders and are included in the denominator when calculating the response rate.

The ORR, with 95% CI, will be summarized for each treatment arm. ORR will be compared between Arm A and Arm B using a CMH test stratified by the randomization strata.

4.4.2.2 Progression-Free Survival per Investigator Assessment

PFS per Investigator assessment is defined according to the same criteria (iwCLL 2018 criteria) and will be analyzed using the same methodology as for the PFS per IRC assessment in Section 4.3.2.

4.4.2.3 Overall Response Rate With or Without Inclusion of PR-L Per Investigator Assessment

The ORR according to Investigator-assessed BOR per iwCLL 2018 criteria will also be evaluated using the same analyses planned for IRC-assessed ORR in Section 4.4.1.1.2. ORR including PR-L assessed by both Investigator and IRC will be analyzed with the same analyses planned for ORR assessed by IRC in Section 4.4.1.1.2.

The concordance for BOR (PR or better, PR-L or better, PD, respectively) assessed by the Investigator and IRC will be provided.

4.4.2.4 Duration of Response (With or Without Inclusion of PR-L)

DoR will be analyzed for patients who achieve a BOR of CR, CRi, nPR or PR. The DoR according to both IRC- and Investigator-assessed BOR will be evaluated.

DoR is defined as the time from the date of the first documented response until the first date of the documentation of PD per iwCLL 2018 criteria, or the date of death from any cause in the absence of documented PD. Patients who are alive and without documented PD at the time of

data cutoff will be censored. Details of the censoring rules are described in Section 6.2.3. DoR analysis will be similar to the main analysis for IRC-assessed PFS in Section 4.3.2.

DoR including PR-L is defined similarly to DoR with the inclusion of PR-L as a response (i.e., PR-L or better). DoR including PR-L assessed by both Investigator and IRC will be analyzed with the same analysis method used for DoR.

4.4.2.5 Event-Free Survival

EFS is defined as the time from randomization to the first occurrence of:

- Documented disease progression per iwCLL 2018 criteria as assessed by Investigator; or
- Initiation of subsequent anticancer therapy for CLL/SLL; or
- Unacceptable toxicity leading to treatment discontinuation as assessed by the Investigator; or
- Death (due to any cause).

EFS analysis will be similar to the primary analysis for IRC-assessed PFS in Section 4.3.2. The table in Section 6.2.4 defines censoring rules to be applied to the EFS analysis.

4.4.2.6 Time to Next Treatment

TTNT is defined as time from the date of randomization to the date of initiation of the subsequent anticancer therapy for CLL/SLL, therapy of pirtobrutinib for Arm B patients who crossover, or death due to any cause, whichever occurs first. For patients who have not received the next anticancer therapy and are still alive or lost to follow-up at the time of data analysis cutoff, TTNT will be censored at the last date the patient is known to be alive. TTNT analysis will be similar to the main analysis for IRC-assessed PFS in Section 4.3.2. The censoring rules are defined in Section 6.2.5.

4.4.2.7 Patient-Reported Outcomes

Details of planned analysis of TTW of CLL/SLL-related symptoms and TTW of physical functioning will be provided in a separate PRO SAP.

4.6 Safety Analyses

All safety analyses, unless otherwise specified, will be performed using the Safety population and will be analyzed as treated and summarized by treatment arms (Arm A, Arm B), and by IdelaR and BR for Arm B, unless otherwise specified. The safety data during crossover period will be summarized and reported separately.

4.6.1 Extent of Exposure

Exposure of each drug will be summarized by treatment arm for all treated patients based on the following:

- Time on treatment (TOT) is calculated as:
  - pirtobrutinib and idelalisib: (date of last dose – date of first dose + 1) / 30.4375
  - bendamustine and rituximab: (date of last dose – date of first dose + 28) / 30.4375
- Dose intensities
- Dose modifications

Dose intensities of pirtobrutinib and idelalisib will be summarized descriptively as actual dose intensity (ADI), planned dose intensity (PDI) and relative dose intensity (RDI).

- The ADI (mg/day) will be calculated as the actual cumulative dose of each drug received divided by TOT (days).
- The PDI of each drug is defined as follows:

$$\text{PDI (mg/day)} = \text{assigned dose level (mg)/day}$$

- The RDI is the percentage of dose received relative to the planned dose through to treatment discontinuation and is defined as follows:

$$\text{RDI (\%)} = (\text{ADI} / \text{PDI}) \times 100\%$$

Dose intensities of bendamustine and rituximab will be summarized descriptively by RDI (%), which is defined as (total cumulative dose received [mg/m^2]/total dose prescribed [mg/m^2] from cycles 1 to 6 × 100).

The number and percentage of patients with dose reductions, dose interruptions, and dose withholdings will be summarized for each drug with the reason for each dose modification.

All analyses of pirtobrutinib exposure will only be performed for the study treatment period for patients randomly assigned to Arm A. All analyses of idelalisib, bendamustine, and rituximab exposure will be performed for the study treatment period for patients randomly assigned to Arm B. Exposure of pirtobrutinib for Crossover population will be summarized similarly to that of Arm A and reported separately.

4.6.2 Adverse Events

The MedDRA PT derived from the verbatim term will be used when reporting AEs by MedDRA terms. Severity will be measured using the grade defined by the NCI-CTCAE Version 5.0.

TEAEs are events that first occurred or worsened in severity from the first dose of study drug through 30 days (+ 7 days window) after the date of the last dose of study treatment or the first date of starting new anticancer therapy for CLL/SLL, whichever is earlier. TEAE will be summarized by SOC and by decreasing frequency of PT within SOC (all Grade and Grade ≥ 3), by decreasing frequency of PT (all Grade and Grade ≥ 3)

SAEs are any AE that at any dose:

- results in death
- is life-threatening
- requires hospitalization or prolonged of existing hospitalization
- results in disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event

TEAE analyses will include summaries of the following:

- AEs, including severity and possible relationship to study treatment
- SAEs, including severity and possible relationship to study treatment
- AEs leading to dose adjustments
- AEs leading to death
- AEs leading to study treatment discontinuation

4.6.2.1 Adverse Events of Special Interest

AESIs are bleeding, bruising, petechiae and purpura, hemorrhage, anemia, neutropenia, thrombocytopenia, infections, infections without COVID-19, COVID-19, and atrial fibrillation or atrial flutter. Categories of AESI may be modified as the understanding of the safety of pirtobrutinib increases.

4.6.2.2 Adverse Events of Potential Clinical Significance

AEPCS will include: second primary malignancy, second primary malignancy (excluding nonmelanoma skin cancer), nonmelanoma skin cancer, lymphocytosis, tumor lysis syndrome, rash, cardiac failure, supraventricular tachyarrhythmias excluding atrial fibrillation and atrial flutter, ventricular tachyarrhythmias, and hypertension.

4.6.2.3 Consolidated Adverse Events

Consolidated AEs are selected composite AE terms consisting of synonymous PTs to allow meaningful interpretation of the AE data. The final list of AESI, AEPCS, and consolidated AE categories and their respective PTs will be maintained at both compound and study level and reported in the CSR.

AEs for Crossover population will be analyzed similarly and reported separately.

4.6.3 Additional Safety Assessments

4.6.3.1 Deaths

- Summary of deaths (all deaths, deaths on treatment, and deaths within 30 days of last dose of study treatment) and their primary cause (study disease progression, AE, other)
- Listing of TEAEs leading to death
- Deaths for Crossover population will be analyzed similarly and reported separately

4.6.3.2 Laboratory Abnormalities

The severity of laboratory results will be classified according to NCI-CTCAE v5.0 except for LFT. For LFT abnormalities, toxicity grades based on NCI-CTCAE v4.03 will be assigned. The standard LFT panel will consist of ALT, AST, and total bilirubin.

Treatment-emergent changes in laboratory values will be reported for the Safety population. The laboratory toxicity by worst NCI-CTCAE grade and shifts in toxicity grading from Baseline to the worst postbaseline grade will be summarized. Change from Baseline to worst postbaseline and to last postbaseline value will be calculated for each parameter.

4.6.3.3 ECOG Performance Status

The ECOG performance status grade ranges from 0 to 5. The ECOG performance score will be summarized by descriptive statistics. Shift to maximum postbaseline score in ECOG performance score will be summarized by treatment arms.

4.6.3.4 Electrocardiograms

Subject incidence of ECG (QTcF) abnormality at Baseline and postbaseline visits will be summarized for Arm A.

4.6.3.5 Vital Signs

Vital sign measurements will be summarized using descriptive statistics. Systolic and diastolic blood pressure will be graded using NCI-CTCAE Version 5.0. Treatment-emergent abnormal changes in vital signs will be summarized and reported.

4.7 Other Analyses

Unless otherwise specified, all the planned analysis in this section will be based on ITT population.

4.7.1 Other Variables and/or Parameters

4.7.1.1 Demographic and Baseline Characteristics

Demographics, baseline characteristics, and medical history will be reported for the ITT population using descriptive statistics. The variables to be used in the summary of demographics and baseline disease characteristics are detailed in Section 6.1.

4.7.1.2 Prior Anticancer Therapy for CLL/SLL

The following variables will be summarized across patients to characterize the extent of prior therapy:

- Prior systemic therapies
- Prior covalent BTK inhibitor
- Prior venetoclax
- Prior BCL-2 inhibitor
- Prior radiotherapy
- Number of prior lines of therapy

The number of regimens or treatment courses each patient received prior to enrolling this study will be reviewed by a medical reviewer of the reported treatments and their corresponding start and end dates.

The reported medication term for prior therapy, concomitant therapy, or subsequent anticancer therapy for CLL/SLL will be assigned to a therapeutic class and preferred term using the World Health Organization Drug Dictionary.

4.7.1.3 Concomitant Therapy

A summary of standardized names of concomitant medication by treatment arm by decreasing frequency will be generated.

4.7.1.4 Subsequent Anticancer Therapy for CLL/SLL

The numbers and percentages of patients receiving subsequent anticancer therapies for CLL/SLL will be provided by type of therapy (radiotherapy and systemic therapy), by drug class, and/or name.

4.7.1.5 Medical Resource Utilization

Medical resource utilization includes the following categories:

- Number of hospitalizations per person-year
- Number of emergency department visits per person-year
- Number of plasma, whole blood, and packed RBC transfusions per person-year
- Number of platelet transfusions per person-year
- Number of hematopoietic growth factor treatments per person-year

Medical resource utilization will be summarized using descriptive statistics by treatment arm.

4.7.2 Subgroup Analyses

To determine whether the treatment effect is consistent across various subgroups, the between-group treatment effect for the primary efficacy endpoint of PFS assessed by IRC and the key secondary efficacy endpoint of OS will be estimated (with a nominal 95% CI) and plotted using forest plots within each category of the following subgroups when appropriate (defined based on eCRF data unless otherwise specified):

- Age at study entry (< 65 years versus ⩾ 65 years, < 75 years versus ⩾ 75 years, and < 85 years versus ⩾ 85 years)
- Sex (male versus female)
- Race (White, Asian, Black or African American, other)
- Ethnicity (Hispanic or Latino, not Hispanic or Latino, other)
- Region (North America, Europe, Asia, Australia)
- Histology (CLL versus SLL)
- Rai stage (0-II versus III-IV)
- ECOG performance status at Baseline (0-1, 2)
- Prior lines of systemic therapies (1, 2, 3, ≥ 4)
- Receipt of prior BCL-2 treatment (yes, no)
- Receipt of prior venetoclax treatment (yes, no; per IWRS)
- Most recent prior anticancer therapy including covalent BTK inhibitor (yes, no)
- Reason for discontinuation from the most recent prior covalent BTK inhibitor (PD versus toxicity versus other)
- Bulky disease (<5 cm versus ≥ 5 cm, < 10 cm versus ≥ 10 cm)
- β2 microglobulin (mg/L) group at Baseline (≤ 3.5 mg/L, > 3.5 mg/L)

- Intended comparator (IdelaR, BR)

In the event that certain subgroup by treatment arm category contains not at least 1 event, depending on the subgroup, such category may be combined with other category under the subgroup or potentially excluded from the analysis. Additional subgroup analyses may be performed as deemed appropriate.

4.8 Interim Analyses

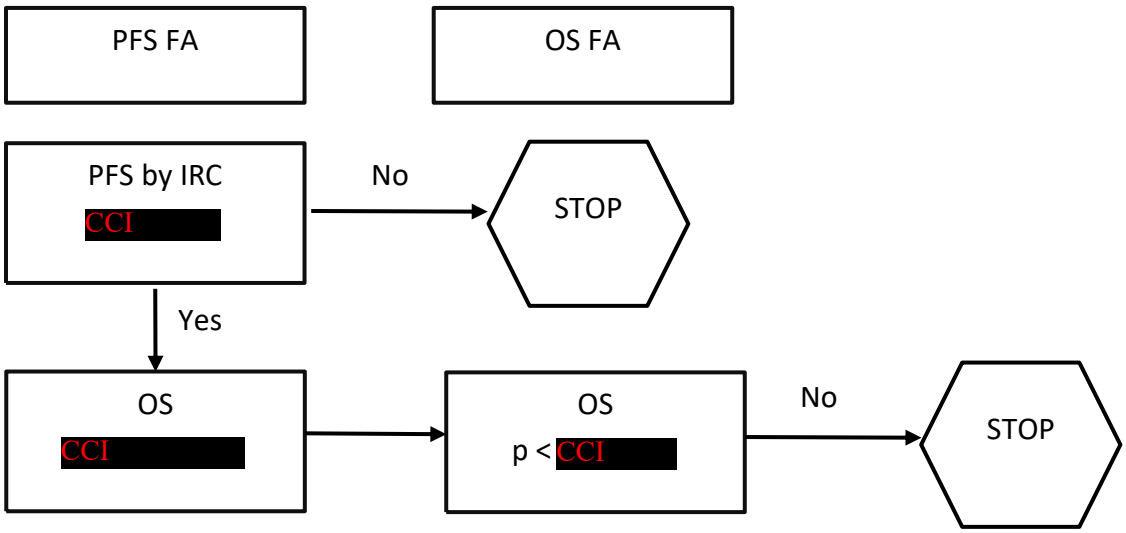
There is no interim efficacy analysis planned for the primary efficacy endpoint IRC-assessed PFS in this study.

4.8.1 Interim Analysis of Overall Survival

A descriptive interim analysis of OS, without formal testing, will be conducted at the time of the IRC-assessed PFS final analysis. An arbitrary CCI will be allocated to the OS to account for early look of OS data and the descriptive analysis planned.

The final analysis of OS will occur approximately CCI months after the primary analysis of PFS to allow adequate follow-up time for OS assessment or when approximately CCI OS events have been observed. TheCCI p-value boundary for the final analysis of OS will be equal to CCI

Figure 1: Diagram of Statistical Testing Procedure for Primary and Key Secondary Efficacy Endpoints



Abbreviations: CCI; p = one-sided p-value; FA = final analysis; IRC = Independent Review Committee; PFS = progression-free survival; OS = overall survival.

* An arbitrary alpha split of CCI is applied

4.8.2 Data Monitoring Committee

An independent DMC will review the safety data periodically and provide recommendations according to the DMC charter. Details are contained in a separate DMC charter.

4.9 Changes to Protocol-Planned Analyses

Changes to the timing of OS analyses as described in the current SAP amendment.

5.0 SAMPLE SIZE DETERMINATION

The sample size of this study was determined (under the assumption of 1:1 randomization) to allow sufficient power for testing IRC-assessed PFS in an error-controlled fashion. For the IRC-assessed PFS, assuming a true HR of CCI IRC-assessed PFS events are required to provide approximately CCI power at a CCI significance level of CCI to reject the null hypothesis (HR = 1.0) using the logrank test. This corresponds to an improvement in median IRC-assessed PFS from CCI months in comparator arm to CCI months for pirtobrutinib arm. Allowing a dropout rate of approximately CCI by the time of primary PFS analysis, the study is expected to enroll approximately 250 patients. The accrual period is assumed to be approximately CCI months, and the final analysis is expected to occur approximately CCI months after the first patient has been randomized.

6.0 SUPPORTING DOCUMENTATION

6.1 Demographic and Baseline Characteristic

6.1.1 Demography

The following variables will be summarized across patients to describe the demographics at enrollment:

- Age at study entry: summarized as a continuous variable in years relative to the date informed consent is signed. Age will also be summarized categorically based on the following age groups:
  - < 50 years
  - 50 to < 65 years
  - 65 to < 75 years
  - 75 to < 85 years
  - ≥ 85 years
  - < 65 versus ≥ 65 years
  - < 75 versus ≥ 75 years
  - < 85 versus ≥ 85 years
- Sex
- Race
- Ethnicity
- Region (North America, Europe, Asian, Australia)
- Height (cm)
- Weight (kg)
- BSA (m2)

6.1.2 Baseline Disease Characteristics

The following variables will be summarized across patients:

- ECOG performance status (0, 1, 2)
- Time (months) from initial diagnosis to first dose
- Histology (CLL, SLL)
- Rai stage (0, I, II, III, and IV)
- Bulky disease (< 5 cm versus ≥ 5 cm; < 10 cm versus ≥ 10 cm)
- β2 microglobulin (mg/L) group at Baseline (≤ 3.5 mg/L, > 3.5 mg/L)

- Cytopenia at Baseline
  - Neutropenia: absolute neutrophil count (ANC) < 1.5 x 10^9/L
  - Anemia: Hgb < 11 g/dL
  - Thrombocytopenia: platelet counts <100 x 10^9/L
  - Any of the above
- Disease-related symptoms (weight loss, fever, night sweats, fatigue)

Additional baseline disease variables may be included.

6.2 Censoring Rules for Time-to-Event Endpoint

6.2.1 Censoring Rules for PFS

Situation	Outcome	Date	Event Description/ Censoring Reason
Documented PD or death on or before data cutoff date:			
Progression documented on or between scheduled visits on or before data cutoff, whichever occurred first	Event	Earliest date of disease assessment documenting progression	PD
Death without documented progression on or before data cutoff	Event	Date of death	Death
Patients without documented PD or death on or before data cutoff date will be censored per censoring rules, unless otherwise specified:			
No documented progression or death on or before of data cutoff	Censored	Date of last adequate disease assessment on or before data cutoff	No documented progression or death at data cutoff
Study discontinuation without documented progression or death	Censored	Date of last adequate disease assessment on or before study discontinuation as reported on end of study CRF	Study exit
Documented progression or death after start of subsequent anticancer therapy	Censored	Date of last adequate disease assessment prior to subsequent anticancer therapy	Event after subsequent anticancer therapy
Subsequent anticancer therapy without documented progression or death	Censored	Date of last adequate disease assessment prior to subsequent anticancer therapy	Subsequent anticancer therapy without event
Documented progression or death immediately after 2 or more consecutively missed scheduled disease assessment visits	Censored	Date of last adequate disease assessment prior to the consecutively missed visits	Event after 2 or more consecutively missed visits
No adequate disease assessment at postbaseline	Censored	Date of randomization	No adequate disease assessment at postbaseline
No radiological tumor assessment at Baseline	Censored	Date of randomization	No baseline tumor assessment

The last adequate disease assessment is defined as the last overall response that is not "UNK" (unknown) for IRC-assessed response and not "NE" (Not Evaluable) for Investigator-assessed response.

6.2.2 Censoring Rules for OS

Situation	Outcome	Date	Event Description/ Censoring Reason
Death on or before data cutoff date	Event	Date of death	Death
Alive at data cutoff	Censored	Date of data cutoff	Alive at data cutoff
Study discontinuation without death on or before data cutoff date	Censored	Date of discontinuation from study participation as reported on end of study CRF	Study exit
Unknown survival status at data cutoff	Censored	Date patient last known to be alive	Unknown survival status

6.2.3 Censoring Rules for DoR

Situation	Outcome	Date	Event Description/ Censoring Reason
Documented progressive disease or death on or before data cutoff date:			
Progression documented on or between scheduled visits on or before data cutoff, whichever occurred first	Event	Earliest date of disease assessment documenting progression	PD
Death without documented progression on or before data cutoff	Event	Date of death	Death
Patients without documented PD or death on or before data cutoff date will be censored per censoring rules, unless otherwise specified:			
No documented progression or death on or before of data cutoff	Censored	Date of last adequate disease assessment on or before data cutoff	No documented progression or death at data cutoff
Study discontinuation without documented progression or death	Censored	Date of last adequate disease assessment on or before study discontinuation as reported on end of study CRF	Study exit
Documented progression or death after start of subsequent anticancer therapy	Censored	Date of last adequate disease assessment prior to subsequent anticancer therapy	Event after subsequent anticancer therapy
Subsequent anticancer therapy without documented progression or death	Censored	Date of last adequate disease assessment prior to subsequent anticancer therapy	Subsequent anticancer therapy without event
Documented progression or death immediately after 2 or more consecutively missed scheduled disease assessment visits	Censored	Date of last adequate disease assessment prior to the consecutively missed visits	Event after 2 or more consecutively missed visits

The last adequate disease assessment is defined as the last overall response that is not “UNK” (unknown) for IRC-assessed response and not “NE” (Not Evaluable) for Investigator-assessed response.

6.2.4 Censoring Rules for EFS

Situation	Outcome	Date	Event Description/ Censoring Reason
Earliest of documented PD, event of interest, or death on or before data cutoff date:			
Progression documented on or between scheduled visits, on or before data cutoff date	Event	Earliest date of disease assessment documenting progression	PD
Treatment discontinuation due to unacceptable toxicity	Event	Date of treatment discontinuation	Treatment discontinuation
Start of subsequent anticancer therapy	Event	Date of initiation of subsequent anticancer therapy	Subsequent anticancer therapy
Death on or before data cutoff	Event	Date of death	Death
Patients without EFS events will be censored on or before data cutoff date:			
No documented progressive disease, no subsequent anticancer therapy received, no treatment discontinuation due to unacceptable toxicity, and no death, on or before data cutoff	Censored	Date of last adequate disease assessment on or before data cutoff	No documented event at data cutoff
Study discontinuation without documented events	Censored	Date of last adequate disease assessment on or before data cutoff	Study exit
No adequate disease assessment available at postbaseline	Censored	Date of randomization	No adequate disease assessment
No radiological tumor assessment at Baseline	Censored	Date of randomization	No baseline tumor assessment

The last adequate disease assessment is defined as the last overall response that is not "NE" (Not Evaluable) for Investigator-assessed response.

6.2.5 Censoring Rules for TTNT

Situation	Outcome	Date	Event Description/ Censoring Reason
Earliest of the following events on or before data cutoff date:			
Start of subsequent anticancer therapy	Event	Date of initiation of subsequent anticancer therapy	Subsequent anticancer therapy
Death on or before data cutoff	Event	Date of death	Death
Start of therapy of pirtobrutinib for Arm B who crossover	Event	Date of initiation of pirtobrutinib for Arm B who crossover	Therapy of pirtobrutinib for Arm B who crossover
Patients without TTNT events will be censored on or before data cutoff date:			
Have not received next anticancer therapy including crossover therapy and are still alive on or before data cutoff	Censored	Date of data cutoff	No documented event at data cutoff
Study discontinuation without documented events	Censored	Date of discontinuation from study participation as reported on end of study CRF	Study exit
Unknown survival status at data cutoff	Censored	Date patient last known to be alive	Unknown survival status

6.3 Algorithms for Handling Partial Dates of Medications

Start Date	Stop Date	Action
Known	Known	If stop date < study drug start date, assign as PRIOR If stop date ≥ study drug start date, and start date ≤ end of treatment, assign as CONCOMITANT If stop date ≥ study drug start date and start date > end of treatment, assign as POSTTREATMENT
	Partial	Impute stop date as latest possible date (i.e., last day of month if day unknown or 31 Dec if day and month are unknown), then: If stop date < study drug start date, assign as PRIOR If stop date ≥ study drug start date, and start date ≤ end of treatment, assign as CONCOMITANT If stop date ≥ study drug start date, and start date > end of treatment, assign as POSTTREATMENT
	Missing or Unknown	If stop date is missing, then PRIOR will never be assumed or assigned If start date ≤ end of treatment, assign as CONCOMITANT If start date > end of treatment, assign as POSTTREATMENT
Partial	Known	Impute start date as earliest possible date (i.e., first day of month if day unknown or 01 Jan if day and month unknown), then: If stop date < study drug start date, assign as PRIOR If stop date ≥ study drug start date and start date ≤ end of treatment, assign as CONCOMITANT If stop date ≥ study drug start date and start date > end of treatment, assign as POSTTREATMENT
	Partial	Impute start date as earliest possible date (i.e., first day of month if day unknown or 01 Jan if day and month are unknown) and impute stop date as latest possible date (i.e., last day of month if day unknown or 31 Dec if day and month are unknown), then: If stop date < study drug start date, assign as PRIOR If stop date ≥ study drug start date and start date ≤ end of treatment, assign as CONCOMITANT If stop date ≥ study drug start date and start date > end of treatment, assign as POSTTREATMENT
	Missing or Unknown	Impute start date as earliest possible date (i.e., first day of month if day unknown or 01 Jan if day and month unknown), then: If stop date is missing, then PRIOR will never be assumed or assigned If start date ≤ end of treatment, assign as CONCOMITANT If start date > end of treatment, assign as POSTTREATMENT
Missing or Unknown	Known	If stop date < study drug start date, assign as PRIOR If stop date ≥ study drug start date, assign as CONCOMITANT If start date is missing, then POSTTREATMENT will never be assumed or assigned
	Partial	Impute stop date as latest possible date (i.e., last day of month if day unknown or: 31 Dec if day and month are unknown), then:

Start Date	Stop Date	Action
		If stop date < study drug start date, assign as PRIOR If stop date ≥ study drug start date, assign as COMCOMITANT If start date is missing, then POSTTREATMENT will never be assumed r assigned
	Missing or Unknown	Assign as CONCOMITANT

6.4 Clinical Trial Registry Analyses

Additional analyses will be performed for the purpose of fulfilling the CTR requirements.

Analyses provided for the CTR requirements include the following:

Summary of AEs, provided as a dataset which will be converted to an XML file. Both SAEs and "Other" AEs are summarized by treatment group and by MedDRA PT.

- An AE is considered "Serious" whether or not it is a TEAE.
- An AE is considered in the "Other" category if it is both a TEAE and is not serious. For each Serious AE and "Other" AE, for each term and treatment group, the following are provided:
  - The number of participants at risk of an event
  - The number of participants who experienced each event term
  - The number of events experienced
- Consistent with www.ClinicalTrials.gov requirements, "Other" AEs that occur in fewer than 5% of patients/subjects in every treatment group may be excluded if a 5% threshold is chosen.
- Adverse event reporting is consistent with other document disclosures, e.g., the CSR, manuscripts, and so forth.

7.0 REFERENCES

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Approval Task	PPD Biostatistics 08-Sep-2023 18:29:05 GMT+0000

Approval Task	PPD Regulatory 08-Sep-2023 21:48:27 GMT+0000

Approval Task	PPD Biostatistics 08-Sep-2023 22:30:15 GMT+0000

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