

Statistical Analysis Plan J2N-OX-JZNP 4.0

A Phase 3 Open-Label, Randomized Study of Pirtobrutinib (LOXO-305) versus Bendamustine plus Rituximab in Untreated Patients with Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (BRUIN CLL-313)

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Compound Number: Pirtobrutinib (LOXO-305)

Short Title: A Phase 3 Study Comparing Pirtobrutinib (LOXO-305) to Bendamustine plus Rituximab in Untreated Patients with CLL/SLL

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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
ANC	absolute neutrophil count
BOR	best overall response
BR	bendamustine with rituximab
BTK	Bruton's tyrosine kinase
C1D1	Cycle 1 Day 1
CI	confidence interval
CLL/SLL	chronic lymphocytic leukemia/small lymphocytic lymphoma
CONSORT	Consolidated Standards of Reporting Trials
CR	complete response
CRF	case report form
Cri	complete response with an incomplete 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
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30
FA	final analysis

Term	Definition
HR	hazard ratio
IA	interim analysis
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IGHV	immunoglobulin heavy chain variable region gene
IPD	important protocol deviations
IR	incidence rate
IRC	Independent Review Committee
IRR	incidence rate ratio
ITT	intention to treat
IV	intravenous(ly)
iwCLL	International Workshop on Chronic Lymphocytic Leukemia
LFT	liver function test
MedDRA	Medical Dictionary for Regulatory Activities
MRU	medical resource utilization
NCI-CTCAE	National Cancer Institute - Common Terminology Criteria for Adverse Events
NED	no evidence of disease
nPR	nodular partial remission
ORR	overall response rate
OS	overall survival
PD	progressive disease
PDI	planned dose intensity
PFS	progression-free survival
PK	pharmacokinetics
PO	orally (<i>per os</i>)
PR	partial response
PR-L	partial response with lymphocytosis

Term	Definition
PRO	patient-reported outcome
PT	preferred term
PYE	patient-years of exposure
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
TTNT	time to next treatment
TTW	time to worsening
UNK	unknown

Version History

This SAP for Study LOXO-BTK-20023 is based on the protocol version 5.0, dated 14 Feb 2024.

Table 1: SAP Version History Summary

SAP Version	Approval Date	Change	Rationale
1.0	Aug 13, 2021	Not Applicable	Original version
2.0	Sep 27, 2021	• Provided details for OS test, including HR assumptions, alpha spending and power in Section 4.8. • Added statistical assessment of the non-proportional hazard assumption used in primary PFS analysis in Section 4.3.2 and in OS analysis in Section 4.4.1. • Added sensitivity analysis of PFS using different censoring rules in Section 4.3.3.	To provide more details for OS test
3.0	June 09, 2025	Clarified the censoring definitions for PFS, OS, DoR, and TTNT endpoints, with clarification of estimand for PFS and estimand for OS. Clarified the definitions of key baseline characteristics. Modified the rules for imputation of missing dates for AEs. Modified the rules for imputation of missing dates for concomitant medications.	To clarify and update to make consistent censoring rules across pirtobrutinib Phase 3 development program. To include biomarker features and other changes to be consistent with subgroup analysis across the CLL programs. To align with eCRF data collection and data standard. To add details about missing data imputation for AE or concomitant medication.

SAP Version	Approval Date	Change	Rationale
		Added 1 sensitivity analysis excluding participants without valid proof of 17p deletion status for PFS analysis. Specified the details for other sensitivity analyses, which were previously specified in a table, in Section 4.3.3.	To examine a potential impact to PFS analysis.
		Specified potential methods to adjust the impact of crossover in OS analysis.	To clarify a sensitivity analysis for OS.
		Updated the alpha spending for the interim and final OS analysis.	To spend less alpha in interim OS analysis and retain more alpha in final OS analysis.
		Clarified calculation of time on treatment.	To clarify time on treatment.
		Added exposure-adjusted incidence rate analysis for AE analysis and clarified AESI and AEPCS terms.	To account for the difference in follow-up between 2 treatment arms.
		Rephrased the analyses of laboratory abnormalities.	To make consistent censoring rules across the pirtobrutinib Phase 3 development program.
		Added details about the evaluation of OS analysis.	To update per FDA feedback and make consistent censoring rules across pirtobrutinib the Phase 3 development program.
		Clarified subgroup analyses for the case of small numbers in a group and updated the potential subgroups for race, ethnicity, region, bulky disease, etc.	To clarify subgroup analyses.

SAP Version	Approval Date	Change	Rationale
		Miscellaneous revisions.	Editorial and formatting changes, minor clarification.
4.0	Refer to date stamp for approval date of current version	Section 1.1.1: Removed the text of definition of TTNT in the table. Section 2: Included the hypothesis for the secondary endpoint of OS. Section 4.4.1.1.3: Added a sensitivity analysis to censor OS at crossover in Arm B participants. Section 4.4.2.2: Included analyses for BOR, concordance and time to response. Section 4.6.1: Updated the 'dose interruption' to 'infusion interruption' and added TOT calculation for ongoing treatment in Arm B. Section 4.7.1.3: Added a summary of subsequent anticancer therapy including crossover treatment. Section 6.2.4: Added 'without documented TTNT events' to 'Unknown survival status at data cutoff date (e.g., lost to follow-up)' and added a note to the table clarifying that subsequent anticancer therapy includes crossover treatment in the TTNT analysis. Section 4.4.2.2: Updated the order of BOR among response.	The full definition of TTNT is in Section 4.4.2.4. To clarify and make consistent with the testing strategy. To add a sensitivity analysis for OS. To clarify the BOR summary. To clarify the extent of exposure analysis. To add an analysis including crossover treatment when summarizing subsequent anticancer therapy. To clarify the event/censoring rule for TTNT, aligning with the TTNT definition. To align with IRC imaging charter.

Abbreviations: AE = adverse event; AEPCS = adverse event of potential clinical significance; AESI = adverse event of special interest; CLL = chronic lymphocytic leukemia; DoR = duration of response; eCRF = electronic case report form; HR = hazard ratio; OS = overall survival; PFS = progression-free survival.

1. Introduction

The purpose of this SAP is to provide details of the statistical analyses for Study LOXO-BTK-20023 (also referred to as BRUIN-CLL-313), which is titled “A Phase 3 Open -Label, Randomized Study of Pirtobrutinib (LOXO-305) versus Bendamustine plus Rituximab in Untreated Patients with Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (BRUIN CLL-313).” A separate SAP will be generated for PK analyses. The biomarkers and their potential correlation to both efficacy and safety may be assessed on a subset of participants and provided in a separate SAP as appropriate.

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	
To evaluate PFS of pirtobrutinib as monotherapy (Arm A) to BR (Arm B).	Assessed by IRC PFS per iwCLL 2018 criteria
Secondary	
To evaluate the effectiveness of Arm A compared to Arm B based on ORR and time to event(s) outcomes.	- Assessed by Investigator: - PFS per iwCLL 2018 criteria - OS - TTNT - Assessed by Investigator and IRC: - ORR - DoR
To evaluate the safety and tolerability of each treatment arm	Incidence and severity of SAEs, AEs, deaths, and clinical laboratory abnormalities per NCI CTCAE v5.0.
To evaluate the effectiveness of Arm A compared to Arm B based on PRO	Patient reported outcomes of: - TTW of CLL/SLL-related symptoms - TTW of physical functioning as measured by the physical function domain of the EORTC QLQ-C30
Tertiary/Exploratory	
To identify biomarkers of response and survival in participants treated in both study arms	Biomarkers assessed from blood, bone marrow and/or tissue samples, unless precluded by local regulations

Objectives	Endpoints
To identify mechanisms of resistance to pirtobrutinib	Clinical outcomes data
To assess use of medical resources including hospitalizations and emergency department visits, transfusions, and growth factor support according to treatment arm	
To explore the relationship between pirtobrutinib plasma exposure and selected efficacy and safety outcomes	
To compare HRQoL measured by EORTC QLQ-C30 and EQ-5D-5L between the treatment arms	

Abbreviations: AE = adverse event; CLL/SLL = chronic lymphocytic leukemia/small lymphocytic lymphoma; DoR = duration of response; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EQ-5D-5L = 5-level version of EQ-5D; HRQoL = health-related quality of life; IRC = independent review committee; iwCLL = International Workshop on Chronic Lymphocytic Leukemia; NCI CTCAE = National Cancer Institute - Common Terminology Criteria for Adverse Events; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PRO = patient-reported outcome; SAE = serious adverse event; TTNT = time to next treatment; TTW = time to worsening.

The estimands are described below following the ICH E9 (R1) addendum ([EMA 2020](#)).

1.1.2. Primary Estimand

The primary research question is: What is the relative treatment effect of pirtobrutinib compared to BR in prolonging PFS in participants with untreated CLL/SLL and no evidence of 17p deletion?

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

- Population: Adult participants with untreated CLL/SLL, no evidence of 17p deletion, and randomized to study intervention. Further details can be found in the protocol, Section 5, Study Population.
- Endpoint: IRC-assessed PFS, which is defined as the time from randomization until documented PD by IRC per iwCLL 2018 criteria or death from any cause, whichever occurs first.
- Treatment condition: The randomized study intervention (pirtobrutinib or BR) will be administered in 28-day cycles until meeting any protocol-defined reason for study discontinuation (protocol Section 7.1) or completing the assigned treatment.
- Intercurrent-event strategies:
 - Subsequent anticancer therapy for CLL/SLL prior to PD or death without PD is handled with hypothetical strategy.

- Extended time without adequate disease assessment (i.e., 2 or more consecutively missed disease assessment visits) is handled with hypothetical 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 versus 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. The participant will be censored and only the time prior to the initiation of the subsequent anticancer therapy will be considered in the analysis.
- PD or death without progression observed after an extended time without adequate disease assessment may have occurred much earlier but was 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, regardless of event status following missed disease assessments, the participant will be censored and only the time up to the last adequate tumor assessment prior to extended time without adequate disease assessment will be considered in the 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 the analysis.

1.1.3. Secondary Estimands

1.1.3.1. Overall Survival

Additional secondary research questions are: What is the relative treatment effect of pirtobrutinib compared to BR in prolonging OS in participants with untreated CLL/SLL and no evidence of 17p deletion?

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

- Population: Adult participants with untreated CLL/SLL, no evidence of 17p deletion, and randomized to study intervention (during the entire study including the crossover period). Further details can be found in the 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 or BR) will be administered in 28-day cycles until any protocol-defined reason is met for study discontinuation (protocol Section 7.1) or the assigned treatment is completed.
- 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 versus BR estimated using a stratified Cox regression model (Cox 1972).
- Rationale for estimand: The interest lies in whether there is treatment benefit in OS comparing pirtobrutinib versus BR regardless of discontinuation, with or without subsequent anticancer therapy for CLL/SLL. Subsequent anticancer therapy for CLL/SLL and study intervention discontinuation due to reasons other than death are handled with treatment policy strategy as it reflects clinical practice for participants.

1.2. Study Design

LOXO-BTK-20023 (BRUIN CLL-313) is a Phase 3, global, multicenter, randomized (1:1), open-label study comparing pirtobrutinib as monotherapy (Arm A) to bendamustine plus rituximab (Arm B) in untreated participants with CLL/SLL.

BRUIN CLL-313 will enroll adult participants with CLL/SLL and no evidence of 17p deletion who require therapy per iwCLL 2018 criteria (Hallek et al. 2018). Eligible participants will be randomized 1:1 to either Arm A or Arm B based on the following stratification factors:

- IGHV mutation status (mutated, unmutated)
- Rai stage (low/intermediate, high)

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

- Arm A: pirtobrutinib (200 mg PO QD) or
- Arm B: bendamustine (6 cycles at 90 mg/m² IV on Days 1 and 2 of each cycle) plus rituximab (375 mg/m² on Day 1 of Cycle 1 and 500 mg/m² on Day 1 of Cycles 2 through 6)

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

Further details of the study design are described in the protocol.

2. Statistical Hypotheses

The primary hypothesis is that the treatment with pirtobrutinib monotherapy will provide superior PFS (assessed by IRC) over treatment with BR in untreated participants with CLL/SLL and no evidence of 17p deletion.

The secondary hypothesis is that the treatment with pirtobrutinib monotherapy will provide superior OS over treatment with BR in untreated participants with CLL/SLL and no evidence of 17p deletion.

2.1. Multiplicity Adjustment

A sequential gate-keeping strategy will be utilized to control the family-wise type I error at 0.05 (two-sided). If the hypothesis test for IRC-assessed PFS is significant, the OS hypothesis will then be tested at two-sided alpha 0.05.

3. Analysis Sets

For purposes of analysis, the following populations are defined:

Population	Description
Entered	All participants who sign informed consent.
ITT	All randomized participants, even if a participant does not take the assigned treatment, does not receive the correct treatment, or otherwise does not follow the protocol. Participants will be analyzed by the treatment arm they were originally assigned, regardless of the treatment they receive. Unless otherwise specified, all analyses using the ITT population will include data only prior to crossover for an Arm B participant who crossed over to Arm A, except for OS related analyses.
Safety	All randomized participants 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 participant 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 an Arm B participant who crossed over to Arm A.
Crossover	A subpopulation of participants 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. Statistical Analyses

4.1. General Considerations

Statistical analysis of this study will be the responsibility of the sponsor or its designee. All tests of treatment effects will be conducted at a 2-sided alpha level of 0.05, unless otherwise stated, and all CIs will be given at a two-sided 95% level, unless otherwise stated. Statistical analysis will be performed using SAS software (SAS, Version 9.4 or higher) or R software (R Version 4.2.2 or higher).

Continuous variables will be summarized using descriptive statistics (i.e., number of participants, 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 participants 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 drug. Baseline measurement of laboratory test will use the last nonmissing measurement prior to the first dose of study drug. Baseline measurement of radiographic imaging will use the last nonmissing measurement prior to randomization.
- **Crossover Period:** The crossover period is defined only for participants 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): $(\text{end date} - \text{start date} + 1)/365.25$
- **Duration of disease:** (randomization date - diagnosis of cancer date + 1).
- **Study Day (safety and tolerability analyses):** Study day is calculated as assessment date – first dose date + 1 day if the assessment is done on or after the first dose 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 Study Day 1.
- **Study Day (baseline and efficacy analyses):** Study day is calculated as assessment date – randomization date + 1 day if the assessment is done on or after randomization. If the assessment is done prior to randomization, study day will be calculated as assessment date – randomization date. Date of randomization is defined as Study Day 1. Study day for Arm B participants will not include the crossover period except for OS related analyses.
- **Study Day for Crossover Period:** Study day for crossover period is only defined for Arm B participants 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 of pirtobrutinib, study day will be calculated as assessment date – first dose date of pirtobrutinib. 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 participant 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, whichever is later, if the onset year is before the year of the first study 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 participant died in the same year, then set the imputed date as the death date.
- If the date of onset 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.
- If the resolution date is completely missing, then no imputation will be done.
- 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 July 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 participant died prior to 15th of the same month to the day.
 - If month is missing, then the date will be set to 01 July of the year, or the date of death if the participant died prior to 01 July 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 participants entered into the study, enrolled in the study, and treated, as well as number and percentage of participants completing the study or discontinuing (overall and by reason for discontinuation).

Participant disposition for the 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, subcategory codes, 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.

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 documented disease progression (per iwCLL 2018 criteria, protocol Section 10.6, Appendix 6) or death from any cause in the absence of documented PD. Participants known to be alive and without PD will be censored at the time of the last adequate disease assessment (detail censoring rules define in Section 6.2.1).

4.3.2. Main Analytical Approach

The analysis of IRC-assessed PFS is event driven. The FA will occur when approximately 53 events have been observed. The IRC-assessed PFS will be compared between treatment arms using a stratified log-rank test, stratified by the randomization strata. The corresponding HR between treatment arms will be estimated using a stratified Cox regression model (Cox 1972). PFS Kaplan-Meier survival curves, medians, and PFS rates at various time points with 95% CI for each treatment arm will be estimated using the Kaplan-Meier method (Kaplan and Meier 1958). The table in Section 6.2.1 defines censoring rules to be applied to the IRC-assessed PFS main analysis.

The assumption of proportionality for Cox regression fit will be assessed. Proportional hazards will be tested firstly by using a time dependent covariate of treatment arm-by-log(time) interaction term in the Cox model and may be checked using graphical methods such as a plot of scaled Schoenfeld residuals against log-transformed time to assess the extent to which this observation represents random variation. If a lack of proportionality is evident, the variation in treatment effect will be examined by presenting piecewise HR calculated over distinct time-periods, for example 0-12 month, 12-24 month etc. Additionally, weighted log-rank test and/or Restricted Mean Survival Time (RMST) methods may be considered.

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 log-rank test and an unstratified Cox regression model.
- Repeat the primary analysis for IRC-assessed PFS stratified by the 2 randomization strata based on the data collected in the case report forms.
- Repeat the primary analysis for IRC-assessed PFS without censoring participants who receive any subsequent anticancer therapy for CLL/SLL prior to the first IRC-confirmed

PD or death due to any cause at the last adequate assessment prior to the start date of the subsequent anticancer therapy for CLL/SLL if there is an adequate disease assessment or death after subsequent anticancer therapy. The presence of subsequent therapy will be handled with the treatment-policy strategy and ignored.

- Repeat the primary analysis for IRC-assessed PFS without censoring participants who have 2 or more consecutively missed disease assessment visits at the last adequate assessment prior to consecutively missed visits if there is an adequate disease assessment or death after the consecutively missed disease assessments. The presence of 2 or more consecutively missed disease assessment visits will be handled with the treatment-policy strategy and ignored. In particular, IRC-confirmed PD or death after 2 or more consecutively missed disease assessment visits will be included as PFS events.
- Repeat the primary analysis for IRC-assessed PFS, excluding participants without a valid test of 17p deletion status at enrollment. A valid result was defined as either a local result or a central result from a peripheral blood sample collected at screening or C1D1 and processed within 96 hours of collection in accordance with the label for the central fluorescence in situ hybridization test (Vysis® CLL Fluorescence in situ Hybridization Probe Kit).

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 participant is alive or lost to follow-up at the time of data analysis, OS data will be censored on the last date the participant is known to be alive.

4.4.1.1.2. Main Analytical Approach

Conditional on achieving a statistical significance for PFS assessed by IRC, OS will be tested at the time of primary analysis (approximately 32 months from the first participant randomized) and at approximately 52 months from the first participant randomized. The details of alpha spending for interim and final analysis of OS are provided in Section 4.8.

The OS analysis will be similar to the main analysis for IRC-assessed PFS in Section 4.3.2, including assessment of the proportional hazards assumption. The table in Section 6.2.2 defines censoring rules to be applied to the OS analysis.

4.4.1.1.3. Sensitivity Analysis

Subsequent anticancer therapy for CLL/SLL (including pirtobrutinib administered at crossover period in Arm B) may significantly impact OS analysis. An OS sensitivity analysis censoring OS at the initiation of subsequent anticancer therapy for CLL/SLL and a sensitivity analysis censoring OS at the initiation of crossover treatment for Arm B participants will be conducted.

Additional sensitivity analyses specifically adjusting for crossover (such as the rank preserving structure failure time model method, inverse probability of censoring weighting method, or two-stage AFT method) may be performed as deemed appropriate.

4.4.2. Supportive Secondary Efficacy Endpoints

4.4.2.1. Progression-free Survival per Investigator Assessment

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

4.4.2.2. Overall Response Rate (with or without Inclusion of PR-L)

ORR is defined as the number of participants 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 participants randomized to each treatment arm. BOR is the best overall response recorded from the start of treatment until PD, in the order of CR, CRi, nPR, PR, PR-L, SD, nonPD, NED, PD, or UNK. Participants who do not have any postbaseline disease response assessments are considered non-responders 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 Cochran-Mantel-Haenszel test stratified by the randomization strata.

The ORR will be evaluated according to both IRC and Investigator-assessed BOR. ORR including PR-L, assessed by Investigator and IRC, will also be analyzed with the same analysis method described above for ORR.

In addition, the number and proportion of participants who achieved each BOR category, the concordance for BOR (PR or better, PR-L or better, respectively), and time to response will be summarized by treatment arms.

4.4.2.3. Duration of Response (with or without Inclusion of PR-L)

DoR will be analyzed for participants 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 (CR, CRi, nPR, or PR) until the first date of the documentation of PD per iwCLL 2018 criteria, or the date of death from any cause, whichever occurs first. The censoring rules for DoR are described in Section [6.2.1](#).

DoR will be analyzed using similar methods as described for the primary analysis of 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.

4.4.2.4. 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 including therapy of pirtobrutinib for Arm B participants who crossover, or death due to any cause, whichever occurs first. The censoring rules for TTNT are described in Section 6.2.4. TTNT analysis will be similar to the primary analysis for IRC-assessed PFS in Section 4.3.2.

4.4.2.5. Patient Reported Outcomes

For each PRO instrument, percentage compliance will be calculated as the number of completed assessments divided by the number of expected assessments at each time point. Data will be separately summarized using descriptive statistics.

TTW in disease-related symptoms and TTW of physical functioning will be analyzed using the similar methods as described for the primary analysis of IRC-assessed PFS in Section 4.3.2. Further details will be provided in the PRO SAP.

Details for each PRO assessment and participant dimension studied, including those intended to evaluate the performance and measurement properties of each assessment or understand the relationship between PROs and other study outcomes, will also be provided in the PRO SAP.

4.5. Tertiary/Exploratory Endpoints Analysis

4.5.1. Pharmacokinetic Analyses

Population PK methods may be used to characterize the PK of pirtobrutinib in this study and any historical data generated to-date. Potential correlations of exposure with dose, demographics, safety, and efficacy outcomes may be assessed. Further details may be described in a separate PK analysis plan.

4.5.2. Biomarkers

Biomarkers assessed from blood or tissue samples and their relationship with clinical outcomes may be analyzed according to a separate translational research analysis plan.

4.5.3. Patient Reported Outcomes

The analysis of PRO exploratory endpoints will be described in the PRO SAP.

4.6. Safety Analyses

All safety analyses, unless otherwise specified, will be performed using the Safety Population and will be summarized by treatment arms.

4.6.1. Extent of Exposure

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

- TOT: For the pirtobrutinib arm, TOT is calculated as (last dose date – first dose date + 1) for participants discontinued from treatment and as (data cutoff date – first dose date + 1) for participants still on treatment. For the BR arm, TOT is calculated as the minimum of (last dose date – first dose date + 28) or (death date – first dose date + 1) for participants discontinued or completed from treatment, and as (data cutoff date – first dose date + 28) for participants still on treatment.
- Dose intensities
- Dose modifications

Dose intensities of pirtobrutinib will be summarized descriptively as ADI, PDI, and RDI.

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

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

Dose intensities of bendamustine and rituximab will be summarized descriptively by RDI (%), which is defined as (total cumulative dose received [mg/m²]/total dose prescribed [mg/m²]) * 100.

The number and percentage of participants with dose reductions, infusion interruptions, and dose holds will be summarized with the reason for each dose modification.

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 after baseline through 30 days (+7-day window) after the date of the last dose of study drug 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 3/4, 5, ≥ 3) and by decreasing frequency of PT (all Grade and Grade 3/4, 5, ≥ 3).

SAEs are any AE that at any dose:

- Results in death
- Is life-threatening
- Requires hospitalization or prolongation 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, including severity and possible relationship to study drug if necessary:

- AEs
- SAEs
- AEs leading to dose modifications, such as dose reduction, withhold or interruption
- AEs leading to death
- AEs leading to study treatment discontinuation

AESIs: bleeding; subcategories of bleeding including bruising, petechiae and purpura; hemorrhage (i.e., bleeding events that do not belong to the other 2 subcategories); anemia, neutropenia; thrombocytopenia; infections (with and without COVID-19 related terms); and atrial fibrillation/atrial flutter. Categories of AESI may be modified as the understanding of the safety of pirtobrutinib increases. The final list of categories will be maintained at both compound and study level and reported in the CSR.

AEPCSs: second primary malignancy (including and 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. Categories of AEPCS may be modified as the understanding of the safety of pirtobrutinib increases. The final list of categories will be maintained at both compound and study level and reported in the CSR.

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

Adverse events for Crossover Population will be analyzed similarly and reported separately.

In addition, summary tables of TEAE with exposure-adjusted IRs will be generated. Exposure-adjusted IR analyses will be based on the following:

- patient-years at risk for a TEAE (PYE), defined as the sum of the years at risk for a TEAE across all participants and calculated as (date of first occurrence of TEAE – first dose date + 1)/365.25 for participants who experience the TEAE and as (end date of the analysis period – first dose date + 1)/365.25 for participants who do not experience the TEAE

- IR per 100 PYE is defined for the first occurrence of a TEAE and is calculated as the number of participants who experience the TEAE divided by PYE times 100, and
- IRR is based on the IR of 1 treatment group relative to the IR of another treatment group. Two-sided p-values and 95% CI for IRR will be based on Poisson regression. When no TEAEs occur in 1 or both treatment groups, the IRR and p-value will be missing.

Additionally, the total patient-years, defined as the sum of the years for the TEAE observation periods across all participants, will be generated.

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 drug) and their primary cause (study disease progression, AE, other)
- Listing of TEAEs leading to death

Deaths for the Crossover Population will be analyzed similarly and reported separately.

4.6.3.2. Laboratory Abnormalities

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. The severity of laboratory results will be classified according to NCI-CTCAE Version 5 except for LFT. For LFT abnormalities, toxicity grades based on NCI-CTCAE Version 4.03 will be assigned. The standard LFT panel will consist of alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and total bilirubin.

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 worst and last postbaseline score in ECOG performance score will be summarized by treatment arms.

4.6.3.4. Electrocardiograms

Subject incidence of ECG abnormality at baseline and postbaseline visits will be summarized by treatment arms.

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 the 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. Concomitant Therapy

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

4.7.1.3. Subsequent Anticancer Therapy for CLL/SLL

The numbers and percentages of participants receiving subsequent anticancer therapies for CLL/SLL will be provided by type of therapy, by drug class and/or name, overall, and by line of therapy. In addition, the summary including crossing over to pirtobrutinib as a subsequent anticancer therapy will be provided.

Note: The reported medication term for 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.

4.7.1.4. Medical Resource Utilization

MRU 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

MRU will be summarized using descriptive statistics by treatment arm. The number and percentage of participants with at least 1 MRU event (e.g., hospitalization, emergency department visit, blood transfusion, platelet transfusion, growth factor use, etc.) during treatment will also be summarized.

4.7.2. Subgroup Analyses

To determine whether the treatment effect is consistent across various subgroups, treatment effect for PFS (with a nominal 95% CI) will be estimated and plotted using forest plots within each category of the following subgroups specified below (defined based on eCRF data unless otherwise specified). If only small numbers of participants are observed in a subgroup within each treatment arm (e.g., < 10), collapsing or omission of subgroups will be considered. P-values for the interaction between the treatment arm and subgroup variables will be reported for descriptive purposes only.

- IGHV mutation (mutated, unmutated), based on central lab at C1D1
- Rai stage (low/intermediate, high)
- Age at enrollment (< 65 years vs. 65 years, < 75 years vs. ≥ 75 years, and < 85 years vs. ≥ 85 years)
- Sex (male vs. female)
- Race (White, Asian, Black or African American, Other)
- Ethnicity (Hispanic or Latino, not Hispanic or Latino, Other)
- Region (North America, South America, Europe, Asia, Australia/New Zealand, Middle East)
- Histology (CLL vs. SLL)
- ECOG performance status at baseline (0, 1, 2)
- Bulky disease (< 5 cm including no measurable lymph node vs. ≥ 5 cm, < 10 cm including no measurable lymph node vs. ≥ 10 cm)
- β_2 microglobulin (mg/L) group at baseline (≤ 3.5 mg/L, > 3.5 mg/L)
- Cytogenetic features (biomarker central laboratory)
 - Presence of 11q deletion (yes, no)
- High risk features (biomarker central laboratory):
 - Complex karyotype (yes, no)
 - TP53 mutation (mutated, unmutated)
 - TP53 mutation or unmutated IGHV (yes, no)

Additional subgroup analyses may be performed as deemed appropriate and necessary.

4.8. Interim Analyses

There is no interim efficacy analysis of PFS planned for this study. However, OS will be analyzed at the time of primary PFS analysis and at the final OS analysis described in Section 4.4.1.1. To maintain the family-wise type I error rate, OS will be tested inferentially for statistical significance only if the test of IRC-assessed PFS is statistically significant, specifically:

- If the test of IRC-assessed PFS is statistically significant at the PFS primary analysis, the IA of OS will be performed.
 - If the OS IA is not significant, a FA of OS will be performed at the end of study.

- If the test of IRC-assessed PFS is not statistically significant, OS will not be tested for statistical significance.

In terms of alpha spending for OS, the cumulative 2-sided alpha will be controlled at 0.05 by splitting alpha as follows. At the time of the interim OS analysis, the nominal 2-sided alpha level for OS will be fixed at 0.000001. The remaining 2-sided alpha 0.049999 will be spent at the FA.

Further details about the evaluation of OS and hypothetical power calculation are described in Section [6.5](#).

4.8.1. 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

Not applicable.

5. 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 0.41, 53 IRC-assessed PFS events are required to provide approximately 90% power at a 2-sided significance level of 5% to reject the null hypothesis ($HR = 1.0$) using the log-rank test. This corresponds to an improvement in median IRC-assessed PFS from 43 months in comparator arm to 105 months for pirtobrutinib arm. Allowing a dropout rate of approximately 10% by the time of primary PFS analysis, the study is expected to enroll approximately 250 participants. The accrual period is assumed to be approximately 16 months, and the dropout rate is assumed to be approximately 10% by the time of primary PFS analysis. The FA is expected to occur approximately 32 months after the first participant has been randomized.

6. Supporting Documentation

6.1. Appendix 1: Demographic and Baseline Characteristics

6.1.1. Demography and Baseline Characteristics

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

- Age at enrollment - 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 vs. ≥ 65 years
 - < 75 vs. ≥ 75 years
 - < 85 vs. ≥ 85 years
- Sex
- Race
- Ethnicity
- Region
- Height (cm)
- Weight (kg)
- Body Mass Index (kg/m²)
- Body Surface Area (m²)

6.1.2. Baseline Disease Characteristics

The following variables will be summarized across participants:

- 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 vs. ≥ 5 cm; < 10 cm vs. ≥ 10 cm). Bulky disease will be defined by the longest diameter among all baseline nodal target lesions identified by the investigator. Subgroups will be defined by thresholds of 5 cm and 10 cm. Participants with no measurable lymph node at baseline will be treated as having a longest diameter of zero in subgroup analyses.
- β_2 microglobulin (mg/L) group at baseline (≤ 3.5 mg/L, > 3.5 mg/L)
- 11q deletion presence (yes, no)

- High risk features:
 - IGHV (mutated, unmutated)
 - Complex karyotype (yes, no)
 - TP53 mutation (mutated, unmutated)
 - TP53 mutation or unmutated IGHV (yes, no)
- Cytopenia at baseline
 - Neutropenia - $ANC \leq 1.5 \times 10^9/L$
 - Anemia - $Hgb \leq 11 \text{ g/dL}$
 - Thrombocytopenia - platelet counts $\leq 100 \times 10^9/L$
 - Any of the above
- Disease related symptoms (weight loss, fever, night sweats, fatigue)

Additional baseline disease variables may be included as deemed appropriate.

6.2. Appendix 2: Censoring Rules for Time to Event Endpoints

6.2.1. Censoring Rules for PFS – Primary Analyses

Situation	Outcome	Date	Event Description/ Censoring Reason
Progression documented on or between scheduled visits, on or before data cutoff	Event	Earliest date of disease assessment documenting progression	PD
Death without documented progression, on or before data cutoff	Event	Date of death	Death
No documented progression or death, on or before data cutoff	Censored	Date of last adequate disease assessment on or before data cutoff or date of randomization, whichever is later	No documented disease progression or death on or before data cutoff
Unless			
Documented progression or death after subsequent anticancer therapy for CLL/SLL	Censored	Date of last adequate disease assessment prior to subsequent anticancer therapy for CLL/SLL or date of randomization, whichever is later	Event after subsequent anticancer therapy
Subsequent anticancer therapy for CLL/SLL without documented progression or death	Censored	Date of last adequate disease assessment prior to subsequent anticancer therapy for CLL/SLL or date of randomization, whichever is later	Subsequent anticancer therapy without event
Documented progression or death after 2 or more consecutively missed disease assessment visits	Censored	Date of last adequate disease assessment prior to the consecutively missed visits or date of randomization, whichever is later	Event after 2 or more consecutively missed disease assessment visits
No documented progression or death after 2 or more consecutively missed disease assessment visits	Censored	Date of last adequate disease assessment prior to the consecutively missed visits or date of randomization, whichever is later	Two or more consecutively missed disease assessment visits without event

Situation	Outcome	Date	Event Description/ Censoring Reason
Study discontinuation without documented PFS events	Censored	Date of last adequate disease assessment or date of randomization, whichever is later	Study exit
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

Abbreviations: CLL/SLL = chronic lymphocytic leukemia/small lymphocytic lymphoma; IRC = independent review committee; PD = progressive disease; PFS = progression-free survival.

Notes: Documented progression can be either IRC- or Investigator-assessed progression, depending on the analysis.

The last adequate disease assessment is defined as the last overall response that is not “UNK” (unknown) for the IRC-assessed response and not “NE” (Not Evaluable) for the Investigator-assessed response. If there are multiple dates associated with 1 assessment, the disease assessment date will be set to the first date when the overall response is PD and the last date otherwise.

6.2.2. Censoring Rules for OS

Situation	Outcome	Date	Event Description/ Censoring Reason
Death on or before data cutoff	Event	Date of death	Death
Alive on or before data cutoff	Censored	Date patient last known to be alive	Alive
Study discontinuation without death, on or before data cutoff	Censored	Date patient last known to be alive	Study exit
Unknown survival status at data cutoff (e.g. lost to follow-up)	Censored	Date patient last known to be alive	Unknown survival status

Abbreviation: OS = overall survival.

6.2.3. Censoring Rules for DoR

Situation	Outcome	Date	Event Description/ Censoring Reason
Progression documented on or between scheduled visits, on or before data cutoff	Event	Earliest date of disease assessment documenting progression, on or after date of first response	PD
Death without documented progression, on or before data cutoff	Event	Date of death, on or after date of first response	Death
No documented progression or death, on or before data cutoff	Censored	Date of last adequate disease assessment on or before data cutoff or date of first documented response, whichever is later	No documented disease progression or death on or before data cutoff
Unless			
Documented progression or death after subsequent anticancer therapy for CLL/SLL	Censored	Date of last adequate disease assessment prior to subsequent anticancer therapy for CLL/SLL or date of first documented response, whichever is later	Event after subsequent anticancer therapy
Subsequent anticancer therapy for CLL/SLL without documented progression or death	Censored	Date of last adequate disease assessment prior to subsequent anticancer therapy for CLL/SLL or date of first documented response, whichever is later	Subsequent anticancer therapy without event
Documented progression or death after 2 or more consecutively missed disease assessment visits	Censored	Date of last adequate disease assessment prior to the consecutively missed visits or date of first documented response, whichever is later	Event after 2 or more consecutively missed disease assessment visits
No documented progression or death after 2 or more consecutively missed disease assessment visits	Censored	Date of last adequate disease assessment prior to the consecutively missed visits or date of first documented response, whichever is later	Two or more consecutively missed disease assessment visits without event

Situation	Outcome	Date	Event Description/ Censoring Reason
Study discontinuation without documented DoR events	Censored	Date of last adequate disease assessment or date of first documented response, whichever is later	Study exit

Abbreviations: CLL/SLL = chronic lymphocytic leukemia/small lymphocytic lymphoma; DoR = duration of response; IRC = Independent Review Committee; PD = progressive disease.

Notes: Documented progression can be either IRC- or Investigator-assessed progression, depending on the analysis. The last adequate disease assessment is defined as the last overall response that is not “UNK” (unknown) for the IRC-assessed response and not “NE” (Not Evaluable) for the Investigator-assessed response. If there are multiple dates associated with 1 assessment, the disease assessment date will be set to the first date when the overall response is PD and the last date otherwise.

6.2.4. Censoring Rules for TTNT

Situation	Outcome	Date	Event Description/ Censoring Reason
Start of subsequent anticancer therapy for CLL/SLL, on or before data cutoff	Event	Date of initiation of subsequent anticancer therapy for CLL/SLL	Subsequent anticancer therapy
Death without subsequent anticancer therapy for CLL/SLL, on or before data cutoff	Event	Date of death	Death
No subsequent anticancer therapy for CLL/SLL and alive, on or before data cutoff	Censored	Date patient last known to be alive	No documented event on or before data cutoff
Unless			
Study discontinuation without documented TTNT events	Censored	Date patient last known to be alive	Study exit
Unknown survival status at data cutoff date (e.g., lost to follow-up) without documented TTNT events	Censored	Date patient last known to be alive	Unknown survival status

Abbreviations: CLL/SLL = chronic lymphocytic leukemia/small lymphocytic lymphoma; TTNT = time to next treatment.

Notes: per the definition of TTNT in Section 4.4.2.4, the subsequent anticancer therapy for CLL/SLL in this table includes therapy of pirtobrutinib for Arm B participants who crossover.

6.3. Appendix 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 $\geq$ study drug start date, and start date $\leq$ end of treatment, assign as CONCOMITANT - If stop date $\geq$ 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): - If stop date < study drug start date, assign as PRIOR - If stop date $\geq$ study drug start date, and start date $\leq$ end of treatment, assign as CONCOMITANT - If stop date $\geq$ 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 $\leq$ 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): - If stop date < study drug start date, assign as PRIOR - If stop date $\geq$ study drug start date and start date $\leq$ end of treatment, assign as CONCOMITANT - If stop date $\geq$ 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): - If stop date < study drug start date, assign as PRIOR - If stop date $\geq$ study drug start date and start date $\leq$ end of treatment, assign as CONCOMITANT - If stop date $\geq$ study drug start date and start date > end of treatment, assign as POSTTREATMENT

Start Date	Stop Date	Action
	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): • If stop date is missing, then PRIOR will never be assumed or assigned • If start date $\leq$ 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 $\geq$ 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): • If stop date $<$ study drug start date, assign as PRIOR • If stop date $\geq$ study drug start date, assign as COMCOMITANT • If start date is missing, then POSTTREATMENT will never be assumed or assigned
	Missing or Unknown	Assign as CONCOMITANT

6.4. Appendix 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 participants/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.

6.5. Appendix 5: Evaluation of OS

OS is considered an important endpoint to inform both safety and efficacy, and an overall interpretation of the benefit-risk profile. It is widely acknowledged that testing treatment effect of OS with strong control of Type I error and adequate power is often not feasible due to limited number of deaths expected during the trial duration.

In this study, a total of 282 participants were randomized 1:1 to Arm A or Arm B. However, assuming a plausible HR of 0.85 in OS under the alternative hypothesis, a 10% dropout rate, and using a log-rank test with 2-sided alpha of 0.05, 1189 events (deaths) are required for 80% power reject the null hypothesis that the HR is equal to 1.

The HR of 0.85 assumed under the alternative hypothesis is reasonable based on the observed HR of 0.89 from the historical Phase III SEQUOIA trial ([Shadman et al. 2025](#)). Further assuming a 60-month OS rate in Arm B of 85.0% (based on [Shadman et al. 2025](#)), the target HR of 0.85 corresponds to a 60-month OS rate of 87.1% in Arm A under the assumption of exponential survival. Following these design assumptions, the table below provides a summary of the operating characteristics for OS analyses using a 2-sided alpha of 0.05 at each planned analysis timepoint, with the OS FA as a benchmark. These calculations demonstrate that the statistical power for a superiority test would be 6.013% with 2-sided alpha of 0.05 at the OS FA.

Power of Overall Survival Analyses

Analysis Timepoint (months)	Expected Number of Deaths at Analysis	Information Fraction (Compared to OS FA)	Rejection Boundary*	Analysis Power*	Probability of Observed HR < 0.9	Probability of Observed HR < 1.0
OS IA at PFS FA (32)	14	56%	0.351	4.887%	0.543	0.619
OS FA (52)	25	100%	0.457	6.013%	0.557	0.658

Abbreviations: FA = final analysis; HR = hazard ratio; IA = interim analysis; PFS = progression free survival; OS = overall survival.

* Rejection boundary and power are calculated using 2-sided alpha of 0.05 for each OS analysis. The actual alpha spend is guided by the testing scheme described in Section 4.8.

To help assess the potential harm for OS, the estimated HR and its 95% CI will be calculated at each OS analysis. The table below provides the probability of observing a HR > 1 at each planned OS analysis under various scenarios when the true HR is greater than 1, accounting for different predicted number of events at each OS analysis under different true HR scenarios. For example, at OS IA, if the true OS HR is 1.05, then the observed HR of OS would lie above 1.0 with probability of 0.538. At OS FA, the predictive probability is defined as the probability that the HR is greater than 1, given the observed HR at the OS IA. For example, if the observed OS HR at the OS IA is 1.05, then the predictive probability that the observed HR at the OS FA is greater than 1 is 0.555.

Probability of Observing a HR > 1.0 at the Planned OS Analyses

OS IA at PFS FA		OS FA	
True HR	Probability	Observed HR at OS IA	Predictive Probability*
1.00	0.500	1.00	0.500
1.05	0.538	1.05	0.555
1.10	0.573	1.10	0.605
1.15	0.610	1.15	0.662
1.20	0.642	1.20	0.703
1.25	0.672	1.25	0.739
1.30	0.706	1.30	0.790
1.35	0.732	1.35	0.817

Abbreviations: FA = final analysis; HR = hazard ratio; IA = interim analysis; PFS = progression free survival; OS = overall survival.

* Predictive probabilities at OS FA are calculated under the assumption that the HR observed at OS IA equals the corresponding value with number of events determined by the true HR in the same row.

The numbers in the table above provide guidance for interpreting descriptive OS analyses for potential harm. Formal monitoring boundaries however were not developed, for example using the approach proposed by [Fleming et al. \(2025\)](#), because the small sample size and limited number of OS events expected at each analysis timepoint in this population of previously untreated CLL/SLL participants precluded a monitoring plan with robust statistical properties.

7. References

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