Statistical Analysis Plan for Study PCYC-1116-CA

An Open-label Extension Study in Patients 65 Years or Older with Chronic Lymphocytic Leukemia (CLL) or Small Lymphocytic Leukemia (SLL) Who Participated in Study PCYC-1115-CA (Ibrutinib vs Chlorambucil)

Date: 13 June 2023

Version 1.0

Table of Contents

List of Tables

List of Figures

List of Appendices

1.0 Introduction

This Statistical Analysis Plan (SAP) describes the statistical analyses for the Ibrutinib Study PCYC-1116-CA "An Open-label Extension Study in Patients 65 Years or Older with Chronic Lymphocytic Leukemia (CLL) or Small Lymphocytic Leukemia (SLL) Who Participated in Study PCYC-1115-CA (Ibrutinib vs Chlorambucil)."

The final analysis for Study PCYC-1116-CA intends to summarize the long-term efficacy and safety outcomes of ibrutinib in subjects 65 years or older with CLL or SLL across the overall follow-up period starting from initiation of the parent study PCYC-1115-CA to closure of the extension study PCYC-1116-CA.

To avoid the patient selection bias in assessing long-term outcomes, all 269 randomized subjects in the intent-to-treat (ITT) population of the parent study will be analyzed including those who did not roll-over to the extension study due to death or any other reasons. The SAP will not be updated in case of administrative changes or amendments to the protocol unless the changes impact the analysis.

Unless noted otherwise, all analyses will be performed using SAS Version 9.4 (SAS Institute Inc., Cary, NC 27513) or later under the Windows SAS server.

This SAP includes changes to analyses described in the protocol. Details are outlined in Section 14.1.

2.0 Study Objectives and Design

2.1 Study Objectives

- To monitor progression-free survival (PFS)
- To continue treatment and safety assessment of patients randomized to Arm B (ibrutinib) in Study PCYC-1115-CA (the parent study) who have not progressed at the time of parent study closure
- To follow patients for long-term outcome

- To capture overall response rate (ORR), duration of response (DOR), PFS, overall survival (OS), and time to next therapy (TTNT)
- To fulfill long-term follow-up requirements of randomized patients after closure of the parent study, including OS

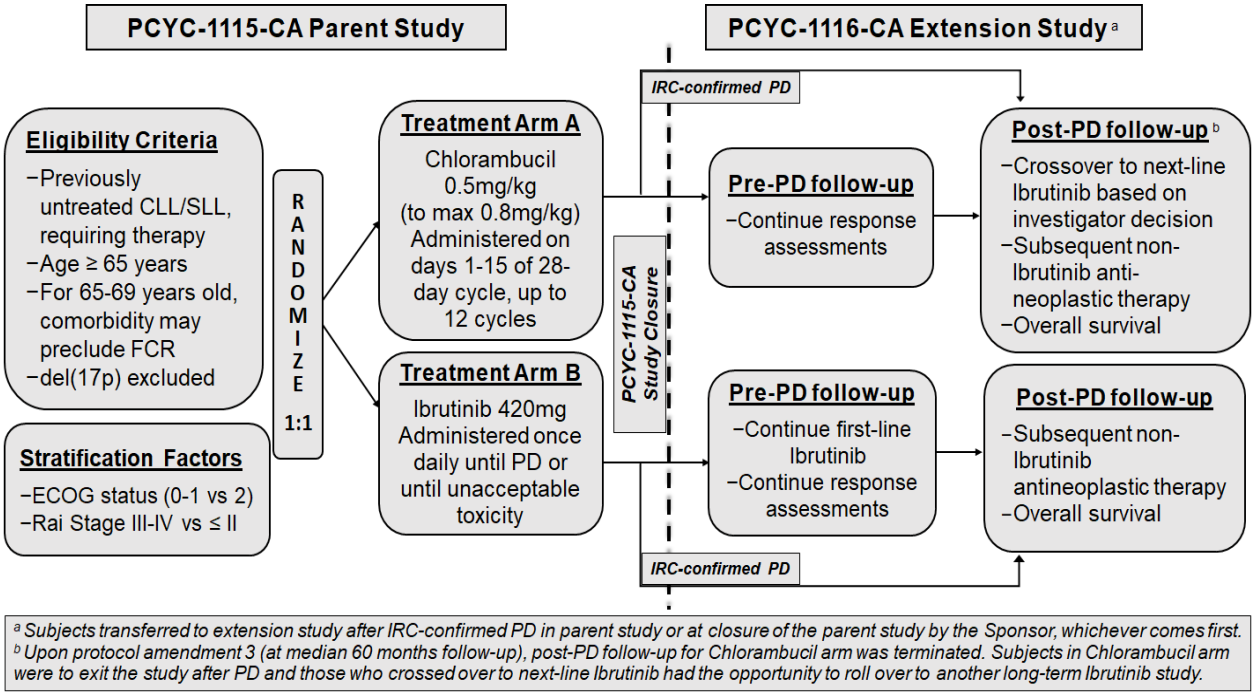
2.2 Study Design Overview

Study PCYC-1116-CA is an open-label, multicenter, extension study of PCYC-1115-CA (parent study) which was initiated concurrently with the parent study. Subjects were transferred to this study after Independent Review Committee (IRC) confirmation of disease progression (PD) in the parent study or at closure of the parent study by Sponsor.

When rollover to Study PCYC-1116-CA occurred, subjects in the chlorambucil arm had either completed or discontinued the first-line chlorambucil treatment and were to be continuing pre-PD response follow-up or were starting post-PD follow-up for subsequent therapy and overall survival; subjects in the ibrutinib arm were to be continuing first-line ibrutinib treatment and/or pre-PD response follow-up, or starting post-PD follow-up, whichever was applicable based on the treatment and response status at the end of participation of the parent study.

The study schematic is shown in Figure 1.

Figure 1. Study Schematic



[a] Subjects transferred to extension study after IRC-confirmed PD in parent study or at closure of the parent study by the Sponsor, whichever comes first.
[b] Upon protocol amendment 3 (at median 60 months follow-up), post-PD follow-up for Chlorambucil arm was terminated. Subjects in Chlorambucil arm were to exit the study after PD and those who crossed over to next-line Ibrutinib had the opportunity to roll over to another long-term Ibrutinib study.

The response and progression were evaluated by the investigator and IRC in accordance with the IWCLL guidelines including clarifications[2-5] from the parent study PCYC-1115-CA and by investigator assessment in the extension study PCYC-1116-CA.

The PCYC-1116-CA study will be closed when approximately 10 years elapsed from the first subject randomized in PCYC-1115-CA. Due to the nature of an extension study, the final analysis for the PCYC-1116-CA clinical study report (CSR) will be based on the pooled clinical database of the parent study and extension study.

2.3 Treatment Assignment and Blinding

Subjects were randomized to ibrutinib or chlorambucil, in a 1:1 ratio at the beginning of the parent study. Randomization of treatment assignment was blocked by geographic region (US versus non-US) and was be stratified by:

- Eastern Cooperative Oncology Group (ECOG) performance status (0, 1 versus 2)
- Presence of advanced-stage disease (Rai stage <3 versus 3-4)

When transferring to the extension study, subjects were to continue the ongoing treatment (if any) from the parent study or initiate subsequent therapy after PD at the discretion of the investigator in the extension study. Crossover to next-line ibrutinib as a subsequent therapy was an option for patients enrolled in the chlorambucil arm only.

Both the parent and extension studies were open label. Neither the subjects nor the investigators were blinded to treatment. However, in the parent study, the Sponsor's staff overseeing the conduct of the study and IRC had been blind to treatment assignment when reviewing or evaluating the efficacy data until the study was closed and its clinical database was locked for analysis. No blinding was performed in the extension study.

2.4 Sample Size Determination

The sample size for the parent study was calculated based on the primary endpoint, PFS, in the parent study (reference to protocol and SAP for study PCYC-1115-CA). No sample size and power calculations were conducted for the extension study PCYC-1116-CA.

The long-term efficacy and safety outcomes for the first-line treatments will be summarized descriptively by arms side-by-side based on the pooled clinical database of parent and extension studies. No hypothesis testing will be performed.

3.0 Endpoints

All primary and secondary endpoints are for first line treatment, unless otherwise specified. PFS, OS, ORR, and minimal residual disease (MRD)-negativity under next-line ibrutinib treatment will be summarized as additional efficacy endpoints.

3.1 Primary Efficacy Endpoint(s)

- Progression Free Survival (PFS)

3.2 Secondary Efficacy Endpoint(s)

3.2.1 Key Secondary Efficacy Endpoints

- Progression Free Survival after initiation of subsequent anticancer therapy (PFS2)
- Overall Survival (OS)
- Time to next treatment (TTNT)
- Overall Response Rate (ORR)
- Rate of MRD Negativity

3.2.2 Supportive Secondary Efficacy Endpoints

- Duration of Response (DOR)

3.3 Additional Efficacy Endpoints

- Progression Free Survival (PFS) after next-line Ibrutinib
- Overall Survival (OS) after next-line Ibrutinib
- Overall Response Rate (ORR) after next-line Ibrutinib
- Rate of MRD Negativity after next-line Ibrutinib

3.4 Safety Endpoint(s)

Safety as measured by TEAEs, laboratory and vital sign measurements.

3.5 Other Endpoint(s)

No other endpoints will be evaluated for this study.

4.0 Analysis Populations

The following population sets will be used for the analyses:

The Intent-to-Treat (ITT) Population as defined in the parent study, PCYC-1115-CA, includes the 269 randomized subjects and will be used for all efficacy and disposition summaries for the first-line therapy, unless otherwise specified. Subjects will be analyzed as randomized.

The safety population includes all subjects in the ITT population who received at least 1 dose of either chlorambucil or ibrutinib as the first-line therapy in the parent study, PCYC-1115-CA. Subjects in the safety population will be analyzed according to the actual treatment received and will be used to summarize the safety (including dosing) for the first-line therapy.

The crossover analysis set includes all chlorambucil-arm subjects who received at least 1 dose of ibrutinib as the next-line study treatment. This analysis set will be used for all efficacy and safety summaries of the next-line ibrutinib.

5.0 Subject Disposition

Subject disposition for each study treatment and for study participation will be tabulated. The overall time on study will be summarized using Kaplan-Meier method with reversed censoring to overall survival (i.e., subjects who died will be censored at death date). The reason for subjects who did not roll over to PCYC-1116-CA study will be summarized separately.

6.0 Study Treatment Duration and Dosing

Exposure to first-line ibrutinib and chlorambucil will be summarized separately for treatment duration and dosing information (e.g., total cumulative dose administered, total number of doses received, average dose level per administration, and relative dose intensity). A similar summary will be provided for the next-line ibrutinib.

7.0 Subject Characteristics

Categorical variables will be summarized with the number and percentage of subjects. Continuous variables will be summarized with descriptive statistics (number of non-missing observations, mean and standard deviation, median, minimum, and maximum).

7.1 Demographics and Baseline Characteristics

All demographics and baseline characteristics were summarized for the ITT population by treatment arm in the PCYC-1115-CA CSR and will not be repeated for the PCYC-1116CA CSR.

7.2 Prior and Concomitant Medications

Medications will be coded to preferred term and Anatomical Therapeutic Chemical (ATC) class according to World Health Organization (WHO) Drug dictionary.

Prior medications are defined as medications that started prior to the first dose date of any study drug from Study PCYC-1115-CA. Concomitant medications for the first-line study treatment are defined as medications that were taken at any time from the first dose date of the first-line study drug through the last dose date of first-line study drug. Concomitant medications for the next-line are defined as medications that were taken at any time from the first dose date of the next-line study drug through the last dose date of next-line study drug.

Concomitant medications will be summarized by therapeutic class and preferred term and by treatment arm for all subjects in the safety population. The following concomitant medications of special interest will be summarized separately: transfusion and growth factors, CYP3A inhibitors and inducers, anticoagulants and/or antiplatelets.

Subsequent CLL/SLL antineoplastic agents taken after the first dosing date of the first-line treatment will be summarized by the regimen type.

7.3 Protocol Deviations

Subjects with important protocol deviations (IPDs) will be identified by the study management team prior to the analysis and will be presented for each treatment arm.

8.0 Handling of Potential Intercurrent Events for the Primary and Key Secondary Endpoints

The following methods noted in Table 1 will be used to address potential intercurrent events for the primary analysis of the primary and key secondary efficacy endpoints (defined in Section 9.0):

Table 1. Handling of Intercurrent Events

Intercurrent Events	Handling Strategies	Applied Endpoints
Premature discontinuation of study drug	Treatment policy strategy Valid assessments and/or follow-up will be used regardless of the study drug discontinuation.	PFS, PFS2, OS, time to next treatment, ORR, DOR, MRD-negativity rate
Use of subsequent anti-cancer therapy	Treatment policy strategy Valid assessments and/or follow-up will be used regardless of use of subsequent anti-cancer therapy.	PFS, OS, DOR
	While on treatment strategy Disease assessments at or prior to initiation of subsequent antineoplastic therapy will be used.	ORR, MRD negativity rate
	Composite strategy Initiating the second subsequent therapy will be considered as a PFS2 event.	PFS2

Intercurrent Events	Handling Strategies	Applied Endpoints
Discontinuation of study before observing an event	Hypothetical strategy Censoring subjects at the last adequate follow-up (last adequate disease assessment for PFS, PFS2 and DOR; last known alive date for OS and time to next treatment)	PFS, PFS2, OS, time to next treatment, DOR
Discontinuation of study without any valid assessments	Composite strategy Discontinuation of study without any valid assessment due to any cause will be considered as non-responders.	ORR, MRD negativity rate

DOR = duration of response; PFS = progression free survival; MRD = Minimal Residual Disease; ORR = overall response rate; OS = overall survival

9.0 Efficacy Analyses

9.1 General Considerations

All efficacy analyses will be conducted on the ITT population, unless otherwise specified.

The extension study was not powered for hypothesis testing. The same between-arm comparisons as for the primary analysis of the parent study will be repeated with the longer-term data in purpose of presenting the relative efficacy benefit descriptively. All p-values are nominal.

Because the response and PD were evaluated by investigator only in the extension study (PCYC-1116-CA), the efficacy endpoints based on response assessments (e.g., PFS, PFS2, ORR, DOR) will be analyzed using the investigator assessments. The outcomes based on IRC assessments are available in the CSR for PCYC-1115-CA.

9.2 Handling of Missing Data

Missing efficacy data will not be imputed, unless otherwise specified. For binary endpoints, subjects who had no baseline and/or post-baseline disease assessment will be

considered as non-responders. For time-to-event endpoints, subjects without any event will be censored on their last adequate assessment for the endpoint. In addition, sensitivity analysis will be performed for the primary endpoint if there is any PFS event that occurred after 2 consecutive missing assessments. Details are specified for each individual endpoint in Section 9.3 and Section 9.4.

9.3 Primary Efficacy Endpoint(s) and Analyses

9.3.1 Primary Efficacy Endpoint(s)

Analysis of the primary endpoint of PFS was conducted on the ITT Population based on treatment as randomized. PFS is defined as the time from the date of randomization to the date of disease progression determined by the investigator or date of death from any cause, whichever occurs first, regardless of the use of subsequent antineoplastic therapy prior to PD or death.

For subjects with baseline and postbaseline response assessments but without investigator-assessed PD and who were not known to have died at the time of the analysis, PFS will be censored at the date of the last adequate disease assessment by the investigator, where adequate disease assessment is defined as physical examination and CBC, or CBC and CT scan within 56 days of each other. For subjects without baseline and/or post-baseline assessments, PFS will be censored on the date of randomization.

9.3.2 Main Analysis of Primary Efficacy Endpoint(s)

The attributes of the estimand corresponding to the primary efficacy objective are summarized in Table 2.

Table 2. Summary of the Estimand Attributes Corresponding to the Primary Efficacy Objectives

	Attributes of the Estimand				
Estimand Label	**Treatment**	**Endpoint**	**Population**	**Handling of Intercurrent Events**	**Statistical Summary**
PFS	Ibrutinib or Chlorambucil	PFS by investigator assessment	ITT population	Valid assessments will be used regardless of study drug discontinuation or use of subsequent anti-cancer therapy. Subjects who did not experience a PFS event as of the analysis will be censored at the last adequate disease assessment date, or randomization date if no baseline or no post-baseline assessment is available.	Distribution of PFS will be estimated by Kaplan-Meier (KM) method for each treatment arm. Median PFS and landmark estimates with 95% confidence interval (CI) will be provided. The hazard ratio (ibrutinib/ chlorambucil) and its 95% CI will be calculated based on a Cox proportional hazard model stratified by the two randomization stratification factors. A nominal p-value will also be calculated by the stratified log-rank test.

9.3.3 Sensitivity and Supplementary Analyses of the Primary Efficacy Endpoint(s)

Sensitivity analyses of the primary efficacy endpoint of PFS will include:

Sensitivity Analysis 1: Unstratified PFS Analysis

An unstratified log rank test will be performed to compare the first-line treatment effect of ibrutinib vs chlorambucil and the hazard ratio (ibrutinib/chlorambucil) along with its 95% CI based on an unstratified Cox model will be provided.

Sensitivity Analysis 2: Censoring PFS Event after 2 or more consecutive missing assessments

Disease progression or death documented immediately after missing two or more consecutive scheduled disease assessments are to be censored at the last adequate disease assessment prior to the consecutive missing assessments in the same stratified analysis as for the primary endpoint.

Supplementary Analysis: Use of subsequent antineoplastic therapy prior to documented PD or death

A supplementary analysis will be performed for the use of subsequent antineoplastic therapy prior to the first documentation of disease progression or death due to any cause: subjects will be censored at the last adequate assessment prior to the use of new antineoplastic therapy.

9.4 Secondary Efficacy Endpoints and Analyses

9.4.1 Key Secondary Efficacy Endpoint(s)

The key secondary endpoints are listed as follows:

- Progression Free Survival after initiation of subsequent anticancer therapy (PFS2): PFS2 is defined as the time from the date of randomization to the earliest occurrence of the following three types of events:
  - PD per investigator response assessment after initiation of the first subsequent anti-cancer therapy
  - Initiation of second subsequent anti-cancer therapy
  - Death due to any cause, regardless of administration of subsequent anticancer therapy.
- Subjects who did not experience a PFS2 event will be censored at the last adequate disease assessment or the last follow-up for subsequent anti-cancer therapy, whichever occurs later.

- Overall survival (OS): OS is defined as the time from randomization to death due to any cause. Subjects who are not known to have died at study closure will be censored at the last date the subject is known to be alive. Subjects who are lost to follow-up without any post baseline assessments/visits will be censored at the date of randomization. All data for subjects on Ibrutinib and Chlorambucil arms collected by the case report form (CRF) will be used for the OS analysis.
- Time to next treatment: Time from randomization to initiation of any subsequent treatment for CLL. Subjects who have not started any subsequent treatment for CLL at the time of the analysis will be censored at the last known alive date.
- Overall Response Rate (ORR): ORR is defined as the proportion of subjects who achieve a CR, CRi, nPR, or PR as determined by the investigator at or prior to initiation of subsequent antineoplastic therapy. Subjects with no post-baseline disease assessment will be considered non-responders.
- Rate of MRD-negativity: Proportion of subjects who achieved MRD-negative response defined as < 1 CLL cell per 10,000 leukocytes as assessed by flow cytometry of a bone marrow aspirate and/or peripheral blood sample per central laboratory at or prior to initiation of subsequent antineoplastic therapy. Subjects with no post-baseline MRD samples will be considered non-responders.

9.4.2 Main Analyses of Key Secondary Efficacy Endpoint(s)

The attributes of the estimands corresponding to the key secondary efficacy objectives are summarized in Table 3.

Table 3. Summary of the Estimand Attributes Corresponding to the Key Secondary Efficacy Objectives

	Attributes of the Estimand				
Estimand Label	**Treatment**	**Endpoint**	**Population**	**Handling of Intercurrent Events**	**Statistical Summary**
PFS2	Ibrutinib or Chlorambucil	PFS after initiation of subsequent anticancer therapy	ITT population	Valid assessments will be used regardless of study drug discontinuation. Subjects who did not experience a PFS2 event will be censored at the last adequate disease assessment or the last follow-up for subsequent anti-cancer therapy, whichever occurs later.	Same as primary endpoint.
OS	Ibrutinib or Chlorambucil	Overall Survival	ITT population	Valid assessments will be used regardless of study drug discontinuation or use of subsequent anti-cancer therapy. Subjects who are not known to be dead will be censored at the last known alive date	Same as primary endpoint.
TTNT	Ibrutinib or Chlorambucil	Time to next treatment	ITT population	Valid assessments will be used regardless of study drug discontinuation. Subjects who are not known to have any subsequent therapy will be censored at the last known alive date.	Same as primary endpoint.

Estimand Label	Attributes of the Estimand				
	Treatment	**Endpoint**	**Population**	**Handling of Intercurrent Events**	**Statistical Summary**
ORR	Ibrutinib or Chlorambucil	Overall Response Rate	ITT population	Valid assessments prior to initiation of subsequent antineoplastic therapy will be used regardless of study drug discontinuation. Discontinuation of study without any valid assessment due to any cause will be considered as non-responders.	Proportion of responders. Rate ratio and 95% CI Cochran-Mantel-Haenszel chi-square test stratified by the two randomization stratification factors.
MRD-negativity rate	Ibrutinib or Chlorambucil	MRD-negativity rate	ITT population	Valid assessments prior to initiation of subsequent antineoplastic therapy will be used regardless of study drug discontinuation. Discontinuation of study without any valid assessment due to any cause will be considered as non-responders.	Proportion for MRD-negativity

Note for Limitation of OS Analysis

According to protocol amendment 3 which was implemented at 60 months median follow up, post PD follow up for Chlorambucil arm was terminated. Subjects in the Chlorambucil arm were to exit study after PD and those who crossed over to next-line ibrutinib had opportunity to rollover to another long-term ibrutinib study. Therefore, the estimate of hazard ratio and log rank test will be impacted and can mainly be used for descriptive purposes. The limitation will be noted in footnote of all related tables and figures, and the landmark estimates for Chlorambucil arm will be limited up to 60 months, while ibrutinib arm will have all meaningful landmark estimates up to study closure (approximately 10 years).

9.4.3 Sensitivity and Supplementary Analyses for Key Secondary Efficacy Endpoints

No additional analysis will be performed for the key secondary endpoints.

9.4.4 Supportive Secondary Efficacy Endpoints and Analyses

- The supportive secondary endpoints are listed below:
  - Duration of Response (DOR): Duration of response will be calculated for the subjects achieving a response (CR, CRi, nPR, PR) per investigator assessment and is defined as time from the date of initial response including PR with lymphocytosis to the date of disease progression or the date of death from any cause, whichever occurs first. For subjects without documented PD or death, DOR will be censored at the date of last adequate disease assessment.
- The attributes of the estimand corresponding to the supportive secondary efficacy objective are summarized in Table 4.

Table 4. Summary of the Estimand Attributes Corresponding to the Supportive Secondary Efficacy Objective

	Attributes of the Estimand				
Estimand Label	**Treatment**	**Endpoint**	**Population**	**Handling of Intercurrent Events**	**Statistical Summary**
DOR	Ibrutinib or Chlorambucil	Duration of Response	ITT subjects achieving response (PR or better) prior to initiation of subsequent antineoplastic therapy	Valid assessments will be used regardless of study drug discontinuation or use of subsequent anti-cancer therapy to identify PD or death event. Subjects who are not known to have PD or death will be censored at the last adequate disease assessment.	KM estimates and 95% CI

9.5 Additional Efficacy Endpoints and Analyses

[redacted]

[redacted]

9.6 Efficacy Subgroup Analyses

Subgroup analysis for PFS may be performed using the prognostic variables at screening or baseline listed in Table 5. The hazard ratio with its 95% CI will be calculated based on unstratified Cox regression model for each subgroup and presented by a forest plot.

Table 5. Subgroup Definition for Efficacy Analysis

Subgroup	Definition of Subgroup
Age	< 70, ≥ 70
Gender	Male, Female
Race	White, Non-White
Geographic Region	US, Non-US
Histological Diagnosis	CLL, SLL
Baseline Rai Stage as recorded in IWRS	Stage 0-II, III-IV
Baseline ECOG as recorded in IWRS	0-1, 2
Bulky Disease	LDi < 5cm, ≥ 5cm
Elevated LDH at Baseline	No (≤ ULN), Yes (> ULN)
Cytopenia at Baseline	Yes, No
Chromosome 11q Deletion	Yes, No
Serum β2- microglobulin	≤ 3.5mg/L, > 3.5 mg/L
IGHV	Unmutated, Mutated

IWRS = Interactive Web Response System; ECOG = Eastern Cooperative Oncology Group; LDi = longest diameter; LDH = lactic acid dehydrogenase; ULN = upper limit of normal; Cytopenia = yes, if platelet count ≤ 100,000/uL, Hgb ≤ 11g/dL, or ANC ≤ 1500/uL is observed; IGHV = immunoglobulin heavy chain variable region

10.0 Safety Analyses

10.1 General Considerations

Safety data will be summarized for the Safety Population. Safety summaries will be presented in accordance with the treatment actually received by subjects. Statistical tests will not be performed for the safety analysis.

Safety summaries will be based on laboratory test results, vital sign measurements, the incidence and severity of adverse events.

10.2 Adverse Events

Adverse events will be summarized and presented using MedDRA. Non-hematological AEs reported by the investigator will be graded according to NCI-CTCAE version 4.03. Hematologic toxicity will be assessed by the IWCLL 2008 guidelines.

Verbatim descriptions of AEs will be coded to a preferred term and mapped to the appropriate System Organ Class using the current version of Medical Dictionary for Regulatory Activities (MedDRA).

10.2.1 Treatment-Emergent Adverse Events

Treatment-emergent adverse events (TEAEs) for the first-line therapy are defined as any AE related or possibly related to the first-line study treatment by investigator or any AE with an onset date that is on or after the first dose date of the first-line study treatment and no more than 30 days after the last dose of the first-line study treatment or initiation of subsequent anti-cancer therapy (including next-line therapy), whichever occurs earlier.

Treatment-emergent adverse events (TEAEs) for the next-line ibrutinib treatment are defined as any AE related or possibly related to the next-line ibrutinib by investigator or any AE with an onset date that is on or after the first dose date of the next-line ibrutinib treatment and no more than 30 days after the last dose of the next-line ibrutinib treatment

or initiation of other anti-cancer therapy subsequent to the next-line ibrutinib study treatment, which occurs earlier.

The number and percentage of subjects experiencing treatment-emergent AEs will be summarized for the first-line therapy and the next-line ibrutinib treatment separately.

10.2.2 Adverse Event Overview

An overview of AEs will be presented consisting of the number and percentage of subjects experiencing at least one event for each of the following AE categories:

- Any treatment-emergent AE
- Any treatment-emergent AE related to study treatment according to investigator
- Any treatment-emergent AE leading to discontinuation of study treatment
- Any treatment-emergent AE leading to dose reduction(s) of study treatment
- Any serious treatment-emergent AE
- Any serious treatment-emergent AE related to study treatment according to investigator
- Any treatment-emergent AE leading to death
- Any major hemorrhage

The overview of AEs will be provided for the first-line therapy and the next-line ibrutinib treatment respectively.

10.2.3 Treatment-Emergent Adverse Events by SOC and/or PT

Treatment-emergent adverse events will be summarized by system organ class (SOC) and/or preferred term (PT) for the first-line therapy and the next-line ibrutinib treatment respectively. Specific adverse events will be counted once for each subject for calculating percentages, unless stated otherwise. In addition, if the same adverse event occurs multiple times within a subject, the highest severity and level of relationship to study treatment will be reported.

10.2.4 Deaths, Serious Adverse Events, and Adverse Events Leading to Study Treatment Discontinuation

Treatment-emergent serious adverse events (SAEs), TEAEs leading to discontinuation of study treatment, and TEAEs leading to death will be summarized by SOC and/or PT for the first-line therapy and the next-line ibrutinib treatment respectively. A listing of all deaths during the entire study period will also be provided.

10.2.5 Adverse Events of Special Interest

Adverse events of special interest listed below will be summarized for the first-line therapy and may also be summarized for the next-line ibrutinib treatment as data warranted. All but atrial fibrillation are grouping terms (definition in Appendix B) and will be summarized by PT in tables respectively. Atrial fibrillation is based on single preferred term and will be included in the TEAE by SOC and/or PT summary tables specified in Section 10.2.3.

- hemorrhage
- major hemorrhage
- other malignancies (treatment emergent and during entire study period separately)
- hypertension
- other cardiac arrhythmia (excluding atrial fibrillation)
- ventricular tachyarrhythmia
- ischemic stroke
- cardiac failure
- sepsis
- interstitial lung disease (ILD)
- atrial fibrillation

10.3 Analysis of Laboratory Data

All laboratory values will be converted to SI units and classified as normal, low, or high based on normal ranges. Hematologic parameters will be assessed by the IWCLL guidelines for grading hematologic toxicity in CLL studies. All other gradable laboratory parameters will be graded using the NCI CTCAE v4.03 or higher.

Unless otherwise specified, only baseline and post-baseline lab values collected on or after the first dose date of the first-line study treatment and within 30 days after the last dose of the first-line study treatment or initiation of subsequent anti-cancer therapy (including next-line therapy), whichever occurs earlier, will be included in the analysis.

For selected hematology and chemistry laboratory parameters, a summary of worst post-baseline toxicity grade will be provided. Only subjects whose grades worsened post-dose are counted in the numerator of percentage calculation while denominator is the safety population in each treatment arm.

Abnormalities in uric acid and liver function will also be summarized. Shifts tables will be created for creatinine clearance.

10.4 Analysis of Vital Signs

Vital sign measurements of systolic and diastolic blood pressure, and heart rate will be summarized.

Over-time summary statistics (mean, standard deviation, median and range) of vital signs will be tabulated.

11.0 Other Analyses

Subjects impacted by the ongoing COVID-19 pandemic may be summarized in data tables and/or listings as data warranted.

12.0 Interim Analyses

- No interim analysis was planned.

13.0 Overall Type-I Error Control

No hypothesis testing will be performed for this study. Efficacy endpoints will be analyzed in the same method as for PCYC-1115-CA primary analysis for presenting long-term efficacy outcomes. Nominal 2-sided p-values will be calculated without adjustment of multiplicity.

14.0 Version History

Table 6. SAP Version History Summary

Version	Date	Summary
1.0	13 June 2023	Initial version

14.1 Changes to Planned Analyses in the Protocol

The endpoint "Disease outcome following cessation of ibrutinib therapy after attainment of minimal residual disease (MRD)-negative remission in those subjects receiving ibrutinib as second-line therapy" prespecified in the protocol will not be analyzed. The decision was made because only two subjects achieved MRD negativity in peripheral blood on next-line ibrutinib with up to 9-year study follow-up and none of them stopped ibrutinib treatment after attainment of MRD negativity.

The MRD negativity rate for first-line treatment and the next-line ibrutinib will be summarized respectively.

15.0 References

1. Bhattacharya S, Fyfe G, Robert J, et al. Role of sensitivity analyses in assessing progression-free survival in late-stage oncology trials. J Clin Oncol. 2009;27(35):5958-64.
2. Cheson BD, Byrd JC, Rai KR, et al. Novel targeted agents and the need to refine clinical end points in chronic lymphocytic leukemia. J Clin Oncol. 2012;30(23):2820-2.
3. Hallek M, Cheson BD, Catovsky D, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. Blood. 2008; 111(12):5446-56.
4. Hallek M, Cheson BD, Catovsky D, et al. Response assessment in chronic lymphocytic leukemia treated with novel agents causing an increase of peripheral blood lymphocytes. Blood. 2012 (letter; published 4 June 2012). Available from: http://bloodjournal.hematologylibrary.org/content/111/12/5446/reply#bloodjournal_el_6920. Accessed 23 August 2012.
5. Hallek M, Cheson BD, Catovsky D, et al. E-Letter regarding "Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute–Working Group 1996 guidelines": Clarification of iwCLL criteria for a partial response to therapy. Blood. Nov 13 2013.
6. ICH E9 (R1) Addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials, November 2019.
7. DSS Estimand Excellence Working Group. Guidance Document on Estimand Implementation in Study Protocol and Statistical Analysis Plan Version 1.0. 17 October 2022

Appendix A. List of SAP Signatories

Name	Title	Role/Functional Area
[redacted]	Manager, Statistics	Author
[redacted]	Project Director, Biostatistics	Clinical Statistics
[redacted]	Executive Director, Biostatistics	Clinical Statistics
[redacted]	Associate Director, Statistical Programming	Statistical Programming
[redacted]	Senior Medical Director, Clinical Development Oncology	Medical/Scientific Monitor
[redacted]	Senior Director, Regulatory Affairs	Regulatory
[redacted]	Senior Medical Director, PST Lead-Oncology	Safety

Appendix B. Definition of Adverse Events of Special Interest

Adverse Events of Special Interest (AESI) will be identified using the following search criteria:

Area of Safety Interest	Search Criteria
Hemorrhage	Hemorrhage SMQ excluding laboratory terms
Major Hemorrhage	Subset of hemorrhagic events which were ≥ Grade 3, serious, or CNS hemorrhage/hematomas.
Other malignancy	Other malignancies are identified by medical monitor and safety scientist review of preferred terms under the system organ class "Neoplasms benign, malignant and unspecified (incl cysts and polyps)" in MedDRA coding.
Hypertension	Hypertension SMQ narrow search
Other cardiac arrhythmia (excluding atrial fibrillation)	Cardiac arrhythmia SMQ (broad and narrow search) excluding preferred term of "atrial fibrillation"
ventricular tachyarrhythmia	Ventricular tachyarrhythmia SMQ narrow search
ischemic stroke	Ischemic Stroke SMQ narrow search
cardiac failure	cardiac failure SMQ narrow search
Sepsis	preferred terms containing "sepsis," "septic," "bacteremia," "fungaemia" or "viraemia" and excluding the preferred term "septic screen" and those containing "aseptic"
Interstitial Lung Disease (ILD)	ILD SMQ narrow search
Atrial Fibrillation	Preferred Term in MedDRA coding.