Statistical Analysis Plan

Phase 2 study of the combination of ibrutinib plus venetoclax in subjects with treatment-naïve chronic lymphocytic leukemia / small lymphocytic lymphoma

Protocol PCYC-1142-CA

Version: 1.0

Version Date: Feb 18, 2020

Statistical Analysis Plan Approval

Protocol Number:	PCYC-1142-CA
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SAP Version:	1.0
Date:	18Feb2020

By signing below, all parties accept that the analysis methods and data presentations are acceptable and that this document is final.

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ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
ATC	anatomical therapeutic chemical
BM	bone marrow
CBC	complete blood count
CI	confidence interval
CLL	chronic lymphocytic leukemia
CR	complete response
CRi	complete response with incomplete bone marrow recovery
CRR	complete response rate
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DFS	disease free survival
DOCR	duration of complete response
DOR	duration of response
ECOG	Eastern Cooperative Oncology Group
FD	fixed duration
Ibr + Ven	ibrutinib plus venetoclax combination
IGHV	immunoglobulin heavy-chain variable region
IRC	independent review committee
IRT	interactive response technology
IWCLL	international workshop on chronic lymphocytic leukemia
MedDRA	Medical Dictionary for Regulatory Activities
MRD	minimal residual disease
NCI	National Cancer Institute
nPR	nodular partial response
ORR	overall response rate
OS	overall survival
PB	peripheral blood
PD	progressive disease
PFS	progression-free survival
PK	pharmacokinetic
PR	partial response
PRL	PR with lymphocytosis
SAE	serious adverse event
SAP	statistical analysis plan

Abbreviation	Definition
SD	stable disease
SLL	small lymphocytic lymphoma
TEAE	treatment-emergent adverse events
TLS	tumor lysis syndrome
WHO	World Health Organization

1. INTRODUCTION

This statistical analysis plan (SAP) lays out key elements including definitions and statistical methods for analysis of data in evaluation of efficacy and safety for the PCYC-1142-CA study. Analyses of pharmacokinetics (PK) data and exploratory analyses such as for clonal evolution and disease-related mechanisms of resistance will be addressed in separate documents.

Throughout this SAP, "study treatment" and "study drug" are used interchangeably.

1.1. Study Design

This is an international multicenter, 2-cohort Phase 2 study assessing both minimal residual disease (MRD)-guided discontinuation and fixed duration (FD) therapy with the combination of ibrutinib + venetoclax ('Ibr + Ven' hereafter) in subjects with treatment-naïve chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL). Figure 1 outlines the study design.

The MRD cohort begins with the same 15-cycle treatment (3 cycles of ibrutinib single agent lead-in followed by 12 cycles of Ibr + Ven) as in the FD cohort. This is followed by 1 cycle of Ibr + Ven during which MRD-guided randomization occurs, after which treatment proceeds according to the randomization. MRD negativity is assessed by a central laboratory and defined as <1 CLL cell per 10,000 leukocytes ($<1 \times 10^{-4}$), as assessed by flow cytometry of a peripheral blood (PB) or bone marrow (BM) aspirate sample. MRD negativity for randomization purposes must be confirmed serially over at least 3 cycles and must be negative in both bone marrow and peripheral blood.

The randomized treatment for MRD cohort starts from cycle 17 day 1. MRD-negative randomized subjects are randomized to receive double blind ibrutinib or placebo and to be treated until MRD relapse or disease progression (PD) or unacceptable toxicity. MRD-positive randomized subjects are randomized to receive open label ibrutinib or ibrutinib + venetoclax: ibrutinib is to be continued until PD or unacceptable toxicity in either arm, while venetoclax can be administered for up to 2 years cumulatively (including pre-randomization and randomization phases) or until PD or unacceptable toxicity, whichever the earliest.

The FD cohort is an open-label, 1 arm cohort with a fixed duration 15-cycle treatment: 3 cycles of ibrutinib single agent lead-in followed by 12 cycles of Ibr + Ven. This cohort was added in Protocol Amendment 1 after the completion of MRD cohort enrollment. Each cycle consists of 28 days.

All subjects who discontinue treatment in the absence of disease progression will remain on response follow-up until confirmed PD or until study closure. After PD, subjects will be followed for survival and subsequent anti-cancer therapies. Treatment reintroduction is allowed per investigator's discretion for both cohorts as following:

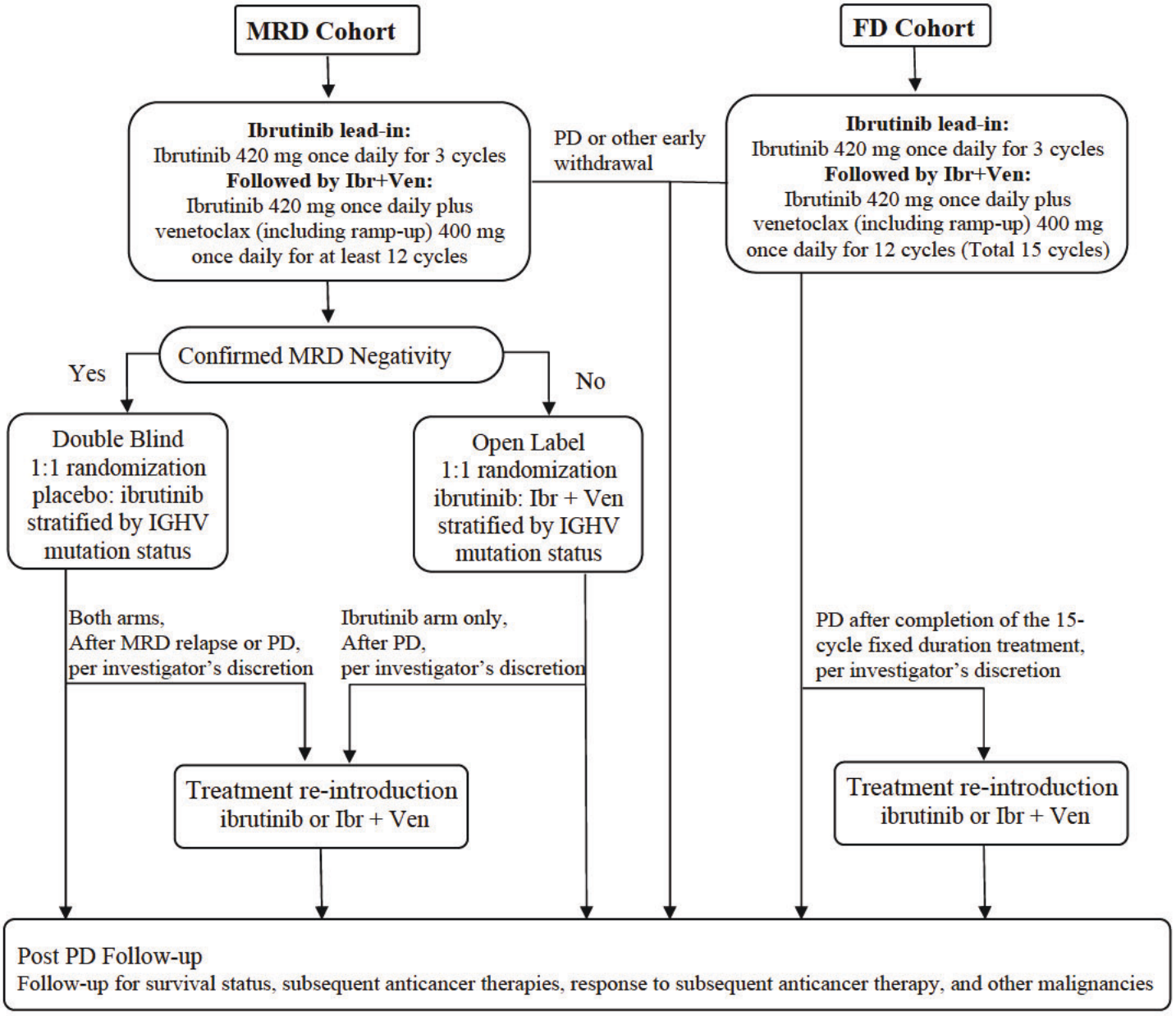
For MRD cohort, treatment reintroduction is allowed for both arms of MRD-negative randomized subjects after MRD-positive relapse and/or PD and for ibrutinib arm only for MRD-positive

randomized subjects after PD. For placebo subjects, ibrutinib is to be reintroduced first and venetoclax may be added further if subsequently PD on reintroduced ibrutinib. Ibrutinib subjects (either MRD-negative randomized or MRD-positive randomized) may continue ibrutinib and reintroduce venetoclax treatment. Reintroduced venetoclax can be administered for up to 2 years.

For FD cohort, subjects with PD after completion of the 15-cycle fixed duration treatment may be retreated by, per investigator's discretion, either continuous single agent ibrutinib until PD or unacceptable toxicity, or a repeat of the fixed duration 15-cycle treatment (3 cycles of ibrutinib single agent lead-in followed by 12 cycles of Ibr + Ven).

Investigators and an independent review committee (IRC) perform the response assessments independently based on radiological imaging, physical examination or other procedures as necessary, hematology results, disease-related symptoms and bone marrow examinations (where appropriate). The response evaluations are in accordance with the International Workshop on Chronic Lymphocytic Leukemia (IWCLL) guidelines (Hallek 2008) including subsequent clarifications (Hallek 2012, Hallek 2013, Cheson 2012).

Figure 1. Study Design



1.2. Endpoints

MRD Cohort	FD Cohort
Primary Endpoint • 1-year disease-free survival (DFS) rate in MRD-negative randomized subjects	**Primary Endpoint** • Complete response (CR/CRi) rate
Secondary Endpoints • MRD negativity rate • Overall response rate • Complete response rate (CR / CRi) • Duration of response • TLS risk reduction • Progression free survival • Overall survival	**Secondary Endpoints** • Duration of response • MRD negativity rate • Overall response rate • TLS risk reduction • Progression free survival • Overall survival
Safety Assessments • Safety and tolerability	**Safety Assessments** • Safety and tolerability
Exploratory Endpoints • [redacted]	**Exploratory Endpoints** • [redacted]

1.3. Statistical Hypotheses

MRD Cohort

The primary objective of this cohort is to evaluate if discontinuing ibrutinib, in the setting of a confirmed MRD-negative response with the combination of ibrutinib + venetoclax (I+V), allows for a treatment holiday as assessed by 1-year disease-free survival.

The statistical hypotheses are as follows:

H_0: The DFS rate at 1-year landmark for experimental treatment group, $S_I(1)$, is equal to the control group, $S_C(1)$:

$$S_I(1) = S_C(1)$$

versus

H_1: The DFS rate at 1-year landmark for experimental treatment group, $S_I(1)$, is different from the control group, $S_C(1)$:

$S_I(1) \neq S_C(1)$

These hypotheses will be tested at 2-sided α level of 0.05 using z test for the difference of two proportions based on Kaplan-Meier estimates with standard error of each arm computed using Greenwood's formula.

FD Cohort

The primary hypothesis of this cohort is that: Complete response rate (CRR) is > 37% after 12-cycle Ibr + Ven treatment.

The statistical hypotheses are as follows:

H_0: CRR ≤ 37%

versus

H_1: CRR > 37%

These hypotheses will be tested at 1-sided α level of 0.025 using asymptotic test for the binomial proportion. Since the assumption for sample size and power of this cohort is based on the historical data of subjects without del 17p, the formal hypothesis testing will be performed on the non-del 17p population (section 2).

1.4. Sample Size Determination

MRD Cohort

The MRD cohort is powered based on the primary endpoint of randomization phase, 1-year DFS rate in MRD-negative randomized subjects (ibrutinib vs placebo). The total sample size will be based on both MRD negativity rate from the Pre-randomization Phase and the sample size assumption from Randomization Phase.

Sixty randomized subjects with confirmed MRD negativity will provide approximately 80% power to detect a 30% improvement in the 1-year disease-free rate, assuming the 1-year disease-free rate is 60% for the control (placebo) arm, at a 2-sided significant level of 0.05.

Assuming a 40% MRD negativity rate for the ibrutinib and venetoclax combination therapy in the Pre-randomization Phase, 150 subjects will be enrolled in the Pre-randomization Phase in order to have 60 subjects achieve confirmed MRD negativity and to be randomized.

FD Cohort

In the FD cohort, assuming the complete response rate for Ibr + Ven is 50%, 125 subjects without del 17p will provide 83% power to ensure the rate is > 37% at 1-side alpha 0.025. A CR rate of 50% would represent meaningful improvement compared to the CR rate seen with the fixed duration combination of bendamustine + rituximab (31%), and would be an improvement over the CR rate seen with the standard of care fixed duration regimen fludarabine, cyclophosphamide and rituximab (40%) which were obtained in the CLL10 study, which included only patients without del 17p (Eichhorst 2016).

The sample size and power calculations were calculated using the software package, East (Cytel Software Corp, Cambridge, MA) version 6.3.

1.5. Planned Analysis

1.5.1. Interim Analysis

No interim analysis was planned or performed for the randomization period of the MRD cohort or for the FD cohort. The protocol prespecified analyses for pre-randomization phase of MRD cohort were completed as follows:

The safety of Ibr + Ven regimen was assessed in safety run-in subjects (the first 14 enrolled MRD cohort subjects) by Data Review Committee (DRC) consisting of the Medical Monitor or designee, a Drug Safety representative, a biostatistician, and at least 2 participating Investigators. DRC meetings were held first on 01May2017 and then on 07Nov2017 when the 6th and the last (i.e. the 14th) safety run-in subjects, respectively, completed the dose limiting toxicity (DLT) evaluation period (defined as the 5-week venetoclax dose ramp-up in combination with ibrutinib plus an additional week of follow up) respectively. No DLT or TLS occurred in safety run-in subjects. The DRC recommended for the study treatment regimen to move forward without modification in both meetings.

To ensure adequate sample size in the MRD-negative randomization, an early assessment of the MRD negativity rate with Ibr + Ven was performed when the first 30 subjects completed 9 cycles of treatment (6 cycles Ibr + Ven) as of the 30Mar2018 data extraction. MRD negativity in PB was achieved in 23 subjects, rate 77% (95% exact binomial confidence interval [CI]: 58% - 90%). The first 14 subjects also completed MRD testing in both PB and BM at cycle 16 as needed to assess for confirmed MRD negative status. Confirmed MRD negativity was achieved in 11 of 14 subjects, rate 79% (95% exact binomial CI: 49% - 95%). The sample size assumption was confirmed, and enrollment continued as planned (section 1.4).

1.5.2. Primary Analysis

The primary analysis for the MRD cohort will be performed after the last randomized subject has the opportunity to receive 1 year of randomized treatment. All safety and efficacy endpoints for MRD cohort will be analyzed at the time of the primary analysis.

The primary analysis for FD cohort will be performed after the last enrolled FD subject has the opportunity to be followed for at least 30 cycles (15 cycles of treatment + 15 cycles of post-treatment follow-up). All safety and efficacy endpoints for FD cohort will be analyzed at the time of the primary analysis. A longer-term analysis for selected MRD cohort endpoints will also be performed using the same data extraction.

The CSR of this study will describe analyses of both MRD and FD cohorts based on data extracted at the time of FD cohort primary analysis. Results for the primary analysis of MRD cohort with earlier data extraction will also be summarized in a report and be documented in the appendix of clinical study report (CSR).

1.5.3. Final Analysis

After the primary analysis of both cohorts, the Sponsor will continue to follow the FD cohort for approximately 5 years after the first subject was enrolled in the cohort and may elect to discontinue follow-up of specific treatment arms of MRD cohort. Subjects who are continuing ibrutinib at the time of study arm closure may be offered a separate extension study to continue ibrutinib. When the study closes, a final analysis will be performed for both cohorts, and a CSR addendum will be prepared.

1.6. Testing Procedure and Level of Significance

For both cohorts, hypothesis testing will be performed independently (without multiplicity adjustment) for the primary endpoint only. Other endpoints will be summarized descriptively with 95% confidence interval (CI) whenever applicable.

- Primary endpoint for MRD cohort, 1-year DFS rate in MRD-negative randomized subjects, will be tested between placebo and ibrutinib arms at a 2-sided alpha level of 0.05.
- Primary endpoint for FD cohort, CRR, will be tested in non-del 17 subjects at a 1-sided alpha level of 0.025.

1.7. Blinding and Randomization Methods

1.7.1. Blinding Method

The FD cohort and Pre-Randomization phase of MRD cohort are an open label single arm study design.

MRD cohort subjects who achieve confirmed MRD negativity after completing the 12 cycle Ibr + Ven treatment will be randomized and treated in a double blind manner. Subjects, investigator and sponsor's study staffs are all blinded to treatment assignment until subject experiences a confirmed MRD-positive relapse or PD event and plans to reintroduce treatment as per protocol. At such time, the specific subject and their treating investigator may request unblinding as needed to make subsequent treatment decisions. The sponsor's independent clinician verifies the DFS event criteria have been met per protocol and approves unblinding on the Interactive Response Technology (IRT) system. Details are described in the Minimizing Bias Document.

MRD cohort subjects who do not achieve confirmed MRD negativity after completing the 12 cycle Ibr + Ven treatment are to be randomized in an open label manner. Neither the subjects nor the investigators are blinded to treatment. However, no aggregated data summary by arm is allowed until data are extracted and approved for the primary analysis for MRD cohort.

In addition to investigator assessment, IRC will evaluate the responses for both cohorts independently. Members of the IRC are blinded to the study treatment for all subjects. The IRC data flow and workflow are detailed in the IRC charter.

1.7.2. Randomization Method

After completing the 12 cycle Ibr + Ven treatment in MRD cohort, subjects will be randomized centrally by two separate schemes according to MRD status, each stratified by IGHV status (Unmutated vs mutated [including borderline or not evaluable]):

- Subjects who achieve confirmed MRD negativity are to be randomized to receive double blind study treatment, either placebo or ibrutinib.
- Subjects who do not achieve confirmed MRD negativity are to be randomized to receive open label treatment, either single agent ibrutinib or Ibr + Ven.

In each scheme, subjects will be randomized in a 1:1 ratio within each randomization stratum. This randomization scheme will be implemented within the IRT system.

2. GENERAL ANALYSIS CONSIDERATION

2.1. Analysis Sets

All treated population includes all enrolled subjects who received at least 1 dose of study drug (ibrutinib or venetoclax or both). All analysis including baseline, disposition, efficacy and safety analysis will be based on this population.

MRD-negative randomized population: defined as all treated subjects in the MRD Cohort who are randomized to the double blind ibrutinib or placebo arms. Subjects in this population will be analyzed according to the treatment to which they are randomized.

MRD-positive randomized population: defined as all treated subjects in the MRD Cohort who are randomized to the open label ibrutinib or Ibr + Ven arms. Subjects in this population will be analyzed according to the treatment to which they are randomized.

Non-del 17p population includes subjects of all treated population without del 17p abnormality according to non-missing baseline FISH results. The primary analysis of the primary and main secondary endpoints for FD cohort will be based on this population.

2.2. Definition of Subgroups

Subgroup analyses will be performed for the selected variables (Table 1) to assess the internal consistency of the treatment benefit. The subgroup variables and the cutoff values may be further modified if warranted.

Table 1: Baseline Subgroups

Baseline Characteristics	Subgroups	Analysis Type
Age	<65 years, ≥65 years	• CRR • MRD negativity rate • Adverse Event
Gender	Male, Female	
Race	White, Non-White	
ECOG score	0, 1-2	• CRR • MRD negativity rate
Rai stage	Stage 0-II, III-IV	
Bulky disease	LDi <5 cm, >=5 cm	
Del 17p	Yes, No	
Del 17p or TP53 mutated	Yes, No	
FISH*	Del 17p, Del 11q, Others	
IGHV per central lab	unmutated, mutated	
Creatinine clearance	<60 mL/min, ≥60 mL/min	• Adverse Event
NCI ODWG Liver Function Classification	Normal, Abnormal	

ECOG = Eastern Cooperative Oncology Group, FISH = Fluorescence in Situ Hybridization,
NCI ODWG= National Cancer Institute Organ Dysfunction Working Group
*Classified in 3 categories per hierarchical order (Dohner et al,2000): del 17p, del 11q without del 17p, and all others (neither del 17p nor del 11q identified).

3. SUBJECT INFORMATION

Subject information will be summarized descriptively. No inferential tests will be performed.

3.1. Subject Disposition

Subject enrollment will be summarized by region, country, site and by cohort. Subject randomization in MRD cohort will be summarized by arm and by stratification factors. Subject disposition for each study treatment and for study participation will be tabulated. The overall duration of receiving any study treatment and time on study will be summarized correspondingly.

Time on study is defined in the same way as overall survival with reversed censoring, i.e. subjects who died will be censored at death date. The Kaplan-Meier method will be used to estimate the median time on study.

3.2. Demographics and Baseline Characteristics

Demographic information and baseline characteristics including but not limited to age, gender, race, histology type, time from initial diagnosis, staging, and potential prognostic factors will be summarized with descriptive statistics.

3.3. 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 study drug. Concomitant medications are defined as medications that were taken at any time on treatment (i.e. from the date of the first dose of study drug through the date of the last dose of study drug).

Concomitant medications will be summarized by therapeutic class and preferred term in the all treated population. The following concomitant medications of special interest will be summarized separately: growth factors, blood supportive products and immunoglobulin, CYP3A inhibitors/inducers, anticoagulants and/or antiplatelet.

3.4. Extent of Exposure to Study Treatment

Exposure to ibrutinib and venetoclax will be summarized separately for treatment duration and dosing information (e.g. total cumulative dose administered, relative dose intensity, ibrutinib or venetoclax dose reduction due to adverse events).

3.5. Subsequent Antineoplastic Therapies

Subsequent CLL/SLL antineoplastic agents will be summarized by type of therapies.

4. ANALYSIS FOR ENDPOINTS

All endpoints will be analyzed in both MRD and FD cohorts separately and pooled except DFS for MRD cohort only. The definition and analysis methods are the same for both cohorts on the same endpoint with some variations on analysis population and analysis period in terms of primary analysis vs supportive analysis of the endpoint.

In general, the analysis population for the primary analysis is the all treated population for the MRD cohort and the non-del17p population for FD cohort. All analyses for the FD cohort will be repeated on the all treated population as supportive analyses.

Unless otherwise specified, the analysis period for primary analysis of endpoints is from the first dose date of study treatment to the first dose date of subsequent antineoplastic therapy or reintroduction of study treatment, whichever occurs earlier, unless otherwise specified. For MRD cohort, this is the overall period including pre-randomization phase and randomization phase. All by-arm summaries of the MRD cohort are also based on the overall period except DFS analyzed within randomization phase only. Summaries for CRR, ORR, MRD negativity rate within the pre-randomization phase (first 16 cycles) in the all treated population of MRD cohort will be provided as supportive analyses.

Table 2 summarizes the efficacy endpoints and analysis methods to be performed. For subgroup and exploratory or supportive analyses, only those providing meaningful information will be presented.

Table 2: Definitions and Analyses for Endpoints

Endpoint	Definition	Analysis Method
Primary Endpoint for MRD Cohort (Not Applicable for FD cohort)		
1-year DFS rate in MRD-negative randomized subjects	DFS will be analyzed in MRD-negative randomized subjects and is defined as time from randomization date to MRD-positive relapse [1], or disease progression per investigator assessment or death from any cause, whichever occurred first. Subjects who do not experience any DFS event will be censored by the last MRD sample date with a valid result [2] or the date of last adequate disease assessment [3] after randomization, whichever occurs earlier. If no valid MRD result and no adequate disease assessment after randomization, DFS will be censored on the randomization date.	Primary The 1-year DFS rates will be estimated using Kaplan-Meier method and the corresponding 2-sided 95% CI will be provided. Z test for the difference of two proportions will be performed based on Kaplan-Meier estimates with standard error of each arm computed using Greenwood's formula. Supportive A log-rank test will be performed for between-arm comparison of DFS distribution. The hazard ratio and its 95% CI based on Cox regression model will be calculated. The 2-year DFS will be explored when median follow-up post randomization >= 2 years.

Endpoint	Definition	Analysis Method
Primary Endpoint for FD Cohort (Secondary Endpoint for MRD cohort)		
Complete response rate (CRR)	The proportion of subjects achieving a best overall response of CR or CRi on or prior to initiation of subsequent antineoplastic therapy or, if applicable, reintroduction of study treatment, whichever occurs earlier.	Primary The point estimate of CRR per investigator assessment and the corresponding 95% CI based on normal approximation to the binomial distribution will be provided. In FD cohort non-del17p population, p value for testing CRR ≤ 37% vs CRR > 37% using asymptotic test for the binomial proportion will be calculated. Sensitivity CRR per IRC assessment. Supportive 1. Duration of complete response (DOCR defined as the interval between the date of initial CR or CRi until disease progression or death from any cause, whichever occurs first.) for subjects who achieved CR or CRi. 2. Durable CRR (defined as proportion of subjects with DOCR >= 336 days (12 cycles)) Subgroup (defined in table 1) The point estimate of CRR per investigator assessment and its 95% CI by normal approximation to the binomial distribution for each subgroup.
Secondary Endpoints for MRD and FD Cohorts		
Overall response rate (ORR)	The proportion of subjects achieving a best overall response of CR, CRi, nPR, or PR on or prior to initiation of subsequent antineoplastic therapy or, if applicable, reintroduction of study treatment, whichever occurs earlier.	Primary The point estimate of ORR per investigator assessment and the corresponding 95% CI based on normal approximation to the binomial distribution will be provided. Sensitivity ORR per IRC assessment.
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 was censored at the date of last adequate disease assessment.	Primary Kaplan-Meier estimates of median DOR time per investigator assessment and landmark estimates with 2-sided 95% CIs. Sensitivity DOR per IRC assessment

Endpoint	Definition	Analysis Method
MRD negativity rate	The proportion of subjects achieving MRD negativity which is defined as <1 CLL cell per 10,000 leukocytes (<1 x 10^{-4}) as assessed by flow cytometry of a peripheral blood (PB) or bone marrow (BM) aspirate sample per central laboratory on or prior to initiation of subsequent antineoplastic therapy or, if applicable, reintroduction of study treatment, whichever occurs earlier.	Primary The point estimate of MRD negativity rate and the corresponding 95% CI based on normal approximation to the binomial distribution will be provided. Sensitivity MRD negativity rate by sample type (PB or BM) Supportive MRD negativity rate by best overall response categories (CR/CRi, nPR/PR/PRL, and all others including non-responders and those off study without response assessment).
Tumor Lysis Syndrome (TLS) risk reduction	The reduction of the proportion of subjects who are at high risk of TLS after the ibrutinib lead-in compared with baseline.	Primary The point estimate of the difference in proportions of subjects with high risk of TLS (at baseline - after ibrutinib lead in) and the corresponding 95% CI (adjusting correlation of paired data) will be provided. Supportive Reduction of the proportion of subjects with hospitalization indicated due to tumor lysis Syndrome (TLS) risk (i.e. subjects with high TLS risk and subjects with medium risk of TLS and creatinine clearance <80 mL/min).
Progression Free Survival (PFS)	Time from the date of first study treatment to the date of disease progression per investigator assessment or date of death from any cause, whichever occurs first, regardless of the use of subsequent antineoplastic therapy prior to documented PD or death. For subjects without documented PD or death, PFS will be censored at the date of last adequate disease assessment. For subjects without adequate disease assessment post-baseline, PFS will be censored on the date of first study treatment.	PFS distribution will be estimated by Kaplan-Meier method: median PFS and landmark estimates with 2-sided 95% CIs will be provided.

Overall Survival (OS)	Time from the date of first study treatment to the date of death from any cause. For subjects who are not known to have died at the time of the analysis, OS will be censored at the date of last known alive.	Kaplan-Meier estimates of median OS time and landmark estimates with 2-sided 95% CIs.
Exploratory Endpoints for MRD and FD Cohorts		
[redacted]		
[1] MRD-positive relapse is defined as an increase in CLL cells ≥1 per 100 leukocytes (≥1 x 10^{-2}) confirmed on two consecutive occasions, after achieving MRD negativity, as assessed by flow cytometry of a PB or BM aspirate sample. [2] MRD samples tested within 5 days after collection are considered valid and can be used in DFS analysis. [3] Adequate disease assessment is defined as physical examination and CBC, or CBC and CT scan within 56 days of each other.		

5. SAFETY ASSESSMENTS

Safety data will be summarized for the all treated population. Table 3 summarizes the safety analyses to be performed.

Adverse events will be coded in accordance with the MedDRA. Severity of AEs will be graded by the investigator according to the NCI-CTCAE v4.03 for non-hematological AEs and IWCLL 2008 guidelines for hematologic toxicity.

Treatment emergent period is defined as the period from the date of the first dose of study treatment up to 30 days after the date of the last dose of study treatment or the day before initiation of subsequent antineoplastic therapy or reintroduction of study treatment, whichever comes first.

The treatment emergent adverse events (TEAE) are those events that occur or worsen during the treatment-emergent period or that are related to the study treatment. Unless otherwise specified, only TEAEs will be included in the adverse event summaries. For MRD cohort, TEAEs within first 16 cycles (pre-randomization phase) and overall treatment emergent period (pre-randomization and randomization phase) will be both summarized.

All laboratory values will be converted to and reported in international system of units (SI). Hematologic parameters including platelet counts, hemoglobin, and neutrophils will be assessed by the grading scale for hematologic toxicity in CLL studies in the IWCLL 2008 guidelines. All other gradable laboratory parameters will be graded using the NCI CTCAE v4.03. Unless otherwise specified, only baseline and post-baseline values collected during the treatment-emergent period will be included in the safety analysis.

Table 3: Summary of Safety Assessments

Assessment Type	Definition	Analysis Methods
AE	TEAEs, SAEs, Grade 3 or worse TEAEs, related TEAEs, TEAEs leading to treatment discontinuation, TEAEs leading to dose reduction, TEAEs leading to death, protocol- defined events of special interest and other safety observations.	Descriptive summary statistics and/or listings
Lab	Worst post-baseline toxicity grade for selected gradable hematology and chemistry. Abnormalities in creatinine clearance, uric acid, and liver function.	Descriptive summary statistics and/or listings
Vital Signs	Blood pressure, heart rate	Descriptive summary statistics and/or listings

TEAE= treatment emergent adverse event; SAE= serious adverse event.

6. CHANGES IN PROTOCOL PLANNED ANALYSIS

- The term “MRD-negative response” was replaced by the phrase “MRD negativity”.

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