Janssen Research & Development

Statistical Analysis Plan

A Randomized, Open-label, Phase 3 study of the Combination of Ibrutinib plus Venetoclax versus Chlorambucil plus Obinutuzumab for the First-line Treatment of Subjects with Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL)

Protocol 54179060CLL3011; Phase 3

JNJ-54179060 (Ibrutinib)

Status: Approved
Date: 16 April 2021
Prepared by: Janssen Research & Development, LLC
Document No.: EDMS-RIM-402082

Compliance: The study described in this report was performed according to the principles of Good Clinical Practice (GCP).

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AMENDMENT HISTORY

Mar 24, 2021 Updated treatment arm abbreviations to "Ibr+Ven" and "Clb+Ob";

Removed "high risk population" analysis set, added it as a subgroup, and updated the definition to include TP53 mutation;

Updated the testing order of secondary endpoints;

Updated analysis methods for primary efficacy endpoint to follow estimand framework;

Added descriptive summary of COVID-19 impact in disposition, safety, protocol compliance, also added sensitivity and/or supplementary analysis for efficacy endpoints;

Updated MRD section to use NGS as the primary method for MRD analysis and two sets of sensitivity analysis to use flow cytometry data; updated the analysis methods for MRD data to include comparison at 3-month and 12-month post end of treatment, and among subjects achieved CR or CRi;

Added descriptive summary of exposure, disposition, AE, etc. for subjects in subsequent therapy phase with single-agent ibrutinib;

Added analysis methods for duration of complete response and Tumor Lysis Syndrome (TLS) risk reduction;

Removed time to response, time to initial response, time to best response from analysis methods for ORR;

Changed all "odds ratio" throughout this SAP to "rate ratio" to be consistent for binary endpoints;

Updated terms to use "study drug" or "study agent" to refer to individual drug and "study treatment" or "study medication" for combination therapy;

Removed subgroup analyses for ORR and OS;

Updated concomitant medication start date imputation rule;

Removed the paragraph on ECG parameters which are not collected in this study;

Updated Table 4 Summary of Adverse Event Analyses to be Performed;

Other editorial changes for clarity.

May 21, 2020 Updated the trial design regarding the duration of treatment in the Ibr+Ven treatment arm and referred to the updated disease evaluation schedule following protocol amendment 2;

Updated the trial design by addition of Subsequent Therapy Phase following protocol amendment 3;

Updated Table 5 Visit Windows for PRO Assessments according to the disease evaluation schedule following protocol amendment 2;

Removed the paragraph on the details of IWRS, which duplicate information in protocol;

Revised the primary efficacy endpoint and analyses in the estimand framework using the final version of ICH E9(R1);

Clarified the timepoint used for the analysis of MRD negativity response rate;

Clarified safety data from Subsequent Therapy Phase will be summarized separately;

Other editorial changes for clarity.

ABBREVIATIONS

AE	adverse event
ALC	absolute lymphocyte count
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ATC	anatomic therapeutic chemical
BM	bone marrow
BSA	body surface area
BTK	Bruton's tyrosine kinase
CBC	complete blood count
CI	confidence interval
CIRS	Cumulative Illness Rating Scale
Clb+Ob	chlorambucil plus obinutuzumab
CLL	chronic lymphocytic leukemia
CMH	Cochran-Mantel-Haenszel
CNS	central nervous system
CR	complete response
CrCl	creatinine clearance
CRF	case report form
CRi	complete response with an incomplete marrow recovery
CSR	clinical study report
CYP	cytochrome p450
DE	disease evaluation
del11q	deletion of the long arm of chromosome 11
DMC	data monitoring committee
DoCR	duration of complete response
DoR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EQ-5D-5L	EuroQol 5 Dimension 5 Level questionnaire
EORTC-QLQ	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire
EOT	end of treatment
FACIT	Functional Assessment of Chronic Illness Therapy
HR	hazard ratio
Ibr+Ven	ibrutinib plus venetoclax
ICH	International Council on Harmonisation
IGHV	immunoglobulin heavy-chain variable region
INR	international normal ratio
IRC	independent review committee
ITT	intent-to-treat
iwCLL	international workshop on Chronic Lymphocytic Leukemia

LDH	lactate dehydrogenase
LDi	longest diameter
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model repeated measures
MRD	minimal residual disease
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NCI-ODWG	National Cancer Institute Organ Dysfunction Working Group
NGS	next-generation sequencing
nPR	nodular partial response
ORR	overall response rate
OS	overall survival
PB	peripheral blood
PD	progressive disease
PFS	progression-free survival
PK	pharmacokinetic(s)
PR	partial response
PRL	partial response with lymphocytosis
PRO	patient-reported outcome(s)
PS	performance status
PT	preferred term
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SI	International System of Units
SLL	small lymphocytic lymphoma
SMQs	standardized MedDRA queries
SOC	system organ class
TEAE	treatment-emergent adverse event
TLS	tumor lysis syndrome
TP53	tumor-suppressor protein 53 gene
ULN	upper limit of normal
VAS	visual analog scale
WBC	white blood count
WHO-DD	World Health Organization Drug Dictionary

1. INTRODUCTION

Ibrutinib is an orally administered, covalently binding inhibitor of Bruton's tyrosine kinase (BTK) for the treatment of B-cell malignancies. This clinical study is designed to evaluate whether the combination of ibrutinib and venetoclax (Ibr+Ven) will result in superior efficacy following a fixed duration of drug administration, compared with the combination of obinutuzumab and chlorambucil (Clb+Ob), in the first-line treatment of subjects with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL).

This statistical analysis plan (SAP) describes the planned statistical analyses for Protocol 54179060CLL3011 (Amendment 4 dated 19 December 2019). It is meant to supplement the study protocol by providing more details on definitions of analysis sets, derived variables, data handling rules and statistical methods for the analysis of efficacy, safety, and patient-reported outcomes. Any deviation from this SAP will be described in the Clinical Study Report (CSR).

1.1. Trial Objectives

Primary objective:

- To compare the progression-free survival (PFS) of Ibr+Ven with that of Clb+Ob as assessed by an Independent Review Committee (IRC).

Secondary objectives:

- To compare the MRD negativity rate of Ibr+Ven with that of Clb+Ob
- To compare the objective response rate (ORR) and complete response (CR) rate of Ibr+Ven with that of Clb+Ob
- To determine the duration of response (DoR)
- To compare the overall survival (OS) of Ibr+Ven with that of Clb+Ob
- To compare the time-to-next treatment of Ibr+Ven with that of Clb+Ob
- To compare the patient-reported health status and fatigue of Ibr+Ven with that of Clb+Ob
- To evaluate the safety profile of Ibr+Ven in subjects with previously untreated CLL/SLL
- To compare the hematologic improvement of Ibr+Ven with that of Clb+Ob
- To evaluate the trough levels of ibrutinib and venetoclax when given in combination

Exploratory objective:

- To examine molecular and protein markers associated with response and relapse following study treatment

1.2. Trial Design

This is a randomized (1:1), open-label, multicenter, Phase 3 study to determine the efficacy and safety of the combination of Ibr+Ven, compared with Clb+Ob, in approximately 200 subjects with previously untreated CLL/SLL who meet the International Workshop on Chronic Lymphocytic Leukemia (iwCLL) treatment criteria [3]. Stratification factors will include the immunoglobulin heavy-chain variable region (IGHV) gene mutational status (mutated vs. unmutated vs. not available) and presence of deletion of the long arm of chromosome 11 ([del11q] yes vs. no).

Subjects randomly assigned to Arm A (Ibr+Ven) will receive study treatment for 15 cycles (1 cycle is 28 days), starting with 3 cycles of ibrutinib monotherapy lead-in and followed by the combination of ibrutinib and venetoclax for 12 cycles (from Cycle 4 through Cycle 15). Subjects randomly assigned to Arm B (Clb+Ob) will receive Clb+Ob for 6 cycles.

Subject participation will include a Screening Phase, a Treatment Phase, and a Follow-up Phase. The Screening Phase will be a period of 30 days before randomization. The Treatment Phase will extend from randomization until study treatment discontinuation. The Follow-up Phase will begin once a subject discontinues treatment. Subjects who discontinue treatment for reasons other than disease progression will continue to have disease evaluations according to Table 3 of protocol.

Subjects from either treatment arm who subsequently develop IRC-confirmed PD and have active disease requiring treatment may be eligible to receive single-agent ibrutinib given until disease progression or unacceptable toxicity as part of the Subsequent Therapy Phase. The Follow-up Phase will continue until death, lost to follow up, consent withdrawal, or study end, whichever occurs first.

The primary analysis and reporting of the study will be conducted after 71 PFS events have been observed. Study end is defined as approximately 5 years after the last subject is randomized into the study or after 50% of subjects have died, whichever occurs first.

Assessment of tumor response and progression will be conducted in accordance with the iwCLL 2008 Guidelines. The investigator will evaluate sites of disease by radiological imaging, physical examination, other procedures as necessary, and review of blood and bone marrow testing (whenever applicable). Disease evaluations will be performed according to Table 3 in protocol. The primary efficacy analysis of PFS will be based on the IRC assessment of PD and death in the intent-to-treat (ITT) population.

During the study, safety evaluations will include adverse event (AE) monitoring, physical examinations, concomitant medication usage, and clinical laboratory parameters (hematology, chemistry, coagulation). At each site visit, subjects will be evaluated for toxicity. Blood samples will be drawn for assessment of pharmacokinetics (Treatment Arm A only) and biomarker parameters. All study evaluations will be conducted according to the Time and Events Schedule in the protocol.

1.3. Statistical Hypotheses for Trial Objectives

The primary efficacy endpoint of this study is PFS. The null statistical hypothesis is that there is no difference in PFS between Ibr+Ven and Clb+Ob as first-line treatment for CLL/SLL subjects:

H_0: The PFS distributions of experimental treatment group, $S_T(t)$, and the control group, $S_C(t)$, are equal at all time points t:

$S_T(t) = S_C(t)$, for all $t > 0$

versus

H_1: The PFS distributions of experimental treatment group, $S_T(t)$, are not equal to that of the control group, $S_C(t)$, for some time point t:

$S_T(t) \neq S_C(t)$, for some $t > 0$

These hypotheses will be tested using the stratified log-rank test as described in Sections 5.

1.4. Sample Size Justification

This study is designed to evaluate the effect of treatment on PFS and is powered for this primary analysis. A median PFS of 27 months is reported for the Clb+Ob when it is used to treat patients with treatment-naïve CLL [2]. It is assumed that the PFS follows an exponential distribution with a constant hazard rate. Utilizing a 1:1 randomization, this study will enroll approximately 200 subjects (100 subjects into Ibr+Ven and 100 subjects into the Clb+Ob treatment groups) to observe 71 PFS events. The study is designed to detect a hazard ratio (HR) of 0.5 for the Ibr+Ven treatment group relative to the Clb+Ob group (corresponding to an improvement of 100% in median PFS, e.g. from 27 months to 54 months) with 80% power at a 2-sided significance level of 0.05.

A uniform accrual rate of 20 subjects per month will result in a study duration of approximately 32 months after the first subject is randomized, with 10 months of enrollment and 22 months of follow-up to observe 71 PFS events.

1.5. Randomization and Blinding

Central randomization will be implemented in this study. Subjects will be randomly assigned to 1 of 2 treatment groups based on a computer-generated randomization schedule prepared before the study under the supervision of the sponsor. The randomization will be balanced by using permuted blocks and stratified by IGHV mutational status (mutated vs. unmutated vs. not available) and presence of del11q (yes vs. no). The block size will be chosen to minimize the chance of accidental unblinding while sufficiently controlling for potential imbalance between treatment groups and will be kept confidential as part of the randomization schedule.

In this open-label study, neither the subjects nor the investigators are blinded to treatment group assignment. However, access to efficacy data is controlled so that the Sponsor's staff overseeing

the conduct of the study or analyzing/summarizing data do not have an aggregated efficacy summary by treatment until the database is locked for primary analysis. The IRC who performs tumor assessment are required to be blinded to study treatment group assignment.

2. GENERAL ANALYSIS DEFINITIONS

2.1. Visit Windows

Throughout this SAP, "study drug" and "study agent" are used interchangeably and apply to individual drug (ibrutinib, venetoclax, chlorambucil, or obinutuzumab), "study medication" and "study treatment" are used interchangeably and apply to the combination therapy of Ibr+Ven or Clb+Ob.

Timing and windowing for study phases and cycles are defined here:

Screening Phase: A period of up to 30 days before the date of first dose of study medication.

Treatment Phase: From the date of first dose of study medication until study treatment discontinuation.

The Treatment Phase will be subdivided by cycles, based on the nominal treatment cycles for the combination therapy as defined in protocol and recorded on the Case Report Form (CRF). The entire combination must be taken into account in defining treatment cycles in a combination therapy setting; hence, a treatment cycle is defined as 28 days.

Follow-up Phase: After the end of treatment until the study cutoff. Cycle-based analysis may be performed for safety parameters during the Treatment Phase up to date of last dose + 30 days or End-of-Treatment visit whichever comes later. For the analysis of lab grade by cycle, worst grade within each cycle will be used.

Subsequent Therapy Phase: From the date of first dose of single-agent ibrutinib until study drug discontinuation. Subjects who develop IRC-confirmed PD and have active disease requiring treatment may be eligible to receive single-agent ibrutinib given until disease progression or unacceptable toxicity as part of the Subsequent Therapy Phase.

2.2. Pooling Algorithm for Analysis Centers

The data from all participating centers in the study will be pooled together for analyses.

2.3. Analysis Sets

2.3.1. Efficacy Analysis Set

The efficacy analysis set is defined as all subjects randomized into the study and who will be analyzed according to assigned treatment group, regardless of the actual treatment received. This is also called intent-to-treat (ITT) population, which will be used for all analyses of primary and

secondary efficacy endpoints and patient-reported outcomes (PROs), analyses of disposition, demographic, and baseline disease characteristics.

2.3.2. Safety Analysis Set

The safety analysis set is defined as all randomized subjects who receive at least one dose of any one of the four study drugs (ibrutinib, venetoclax, chlorambucil, or obinutuzumab). This is also called safety population, which will be used for all safety analyses and analyses of exposure. All subjects will be analyzed according to the treatment which they actually received.

2.3.3. Pharmacokinetics Analysis Set

The pharmacokinetics (PK) analysis set is defined as all randomized subjects in Treatment Arm A who have received at least one dose of ibrutinib and/or venetoclax and had at least one valid blood sample drawn for PK analysis.

2.4. Definition of Subgroups

Subgroup analysis will be performed for the selected variables as shown in Table 1 to assess the internal consistency of the treatment benefit and/or safety. The subgroup variables and the cutoff values are subject to change if warranted to better represent the data.

Table 1: Subgroup Definition

Subgroup	Definition of Subgroup	Analysis Type
Age	<65, ≥ 65 yrs.	D, E, S
Sex	Male, Female	D, E, S
Race	White, Non-White	D, E, S
Diagnosis	CLL, SLL	D
Rai Stage at screening (CLL only)	Stage 0-II, III-IV	D, E
Binet Stage at screening (CLL only)	A, B, C	D, E
Baseline ECOG PS	0, 1-2	E
Cumulative Illness Rating Scale (CIRS) total score	≤6, >6	D, E
Bulky Disease	Yes (LDi ≥5 cm), No (LDi <5 cm),	E
IGHV mutation status	Mutated, Unmutated, Not Available	E
Chromosome 11q Deletion	Yes, No	E
High-risk population	Yes, No	E
Elevated LDH at baseline	Yes (> ULN), No (≤ ULN)	E
Cytopenias at baseline	Yes, No	E
Serum β2–microglobulin	≤3.5 mg/L, >3.5 mg/L	E
Creatinine clearance (CrCl)	<60 mL/min, >=60 mL/min	S
NCI-ODWG Liver Function Classification	Normal, Abnormal	S
Concomitant use of strong/moderate CYP3A inhibitor	Yes, No	S
Concomitant use of strong CYP3A inhibitor	Yes, No	S
High-risk population is defined as yes if subjects present with tumor-suppressor protein 53 gene (TP53) mutation, or del11q or unmutated IGHV status at baseline. Cytopenia is defined as yes if platelet count ≤ 100,000/uL, or Hgb ≤ 11g/dL, or ANC ≤ 1500/uL is observed. Analysis Type D = demographic and baseline disease characteristics Analysis Type E = efficacy (PFS) Analysis Type S = safety (adverse events)		

2.5. Study Day and Relative Day

Assessments will be presented chronologically by study day or cycle day as described below:

Reference date (Day 1) = randomization date (for efficacy data); or date of first dose of study medication (for safety data).

Study Day = assessment date – reference date + 1 for assessment performed on or after the reference date; or assessment date – reference date for assessment performed before the reference date.

Cycle Day = assessment date - date of the first dose for the cycle + 1.

There is no “Day 0”.

2.6. Baseline

Baseline is defined as the last non-missing value collected on or before the administration of the first dose of study medication. For subjects who have been randomized but not treated with any dose, randomization date will be used as the reference date for baseline.

2.7. Imputation Rules for Missing and Partial Dates

In general, imputation of missing dates will be made for AE onset date, AE resolution date, date of death, start and end dates of concomitant and subsequent therapies, and date of initial diagnosis according to the following rules. Start date will be imputed before end date.

- If date is completely missing, no imputation will be made.
- If year is missing, no imputation will be made.
- If only year is present but month and day are missing, then June 30th will be used.
- If only day is missing but year and month are available, then the 15th of the month will be used.

However, the above imputations will be modified by the following rules:

- For initial diagnosis if such imputed date is on or after the randomization date, then randomization date - 1 will be used.
- The imputed start date for subsequent therapies will be adjusted sequentially using the following steps:
    - If the imputed start date is before the treatment discontinuation date (or last dose date if no treatment discontinuation date) but in the same year and month, then the treatment discontinuation date (or last dose date if no treatment discontinuation date) will be used.
    - If subsequent therapy end date is not missing and is before the imputed subsequent therapy start date, then the subsequent therapy end date will be used as the start date.
- If the imputed date is for a date of death and is before the last date that the subject is known to be alive, the latter date will be used.
- The imputed AE start date will be adjusted sequentially using the following steps:
    - If the imputed date is before the first dose date but in the same year and month, then the first dose date will be used, or if it is after the last dose date + 30 days and is in the same year and month, then the last dose date + 30 days will be used.
    - If AE end date is not missing and the imputed AE start date is after the AE end date, then the AE end date will be used.
    - If the imputed AE start date is after date of death, then date of death will be used.

- If the imputed AE start date is in the same month and year, but after the 1st subsequent therapy start date, then 1st subsequent therapy start date will be used.

- If the imputed date is for an AE end date and is after the death date, then the death date will be used, or if the imputed AE end date is before the AE start date, then the AE start date will be used.
- The imputed start date for concomitant medication will be adjusted sequentially using the following steps:
  - If the concomitant medication was taken prior to study start, and the imputed start date is after study treatment start date, further adjust the imputed start date as the day prior to study treatment start date; if the medication was taken after study start, and the imputed start date is prior to study treatment start date, further adjust the imputed start date as study treatment start date.
  - If concomitant medication end date is not missing and is before the imputed concomitant medication start date, then the concomitant medication end date will be used as the start date.

3. INTERIM ANALYSIS AND DATA MONITORING COMMITTEE REVIEW

No formal interim analysis for efficacy is planned due to the small sample size and short accrual period of this study.

An independent DMC is established to monitor data on a regular basis to ensure the continuing safety of the subjects enrolled in this study. The DMC will consist of three medical experts in the relevant therapeutic area and one statistician. The committee will meet periodically to review safety data. After the review, the DMC will make recommendations regarding the conduct of the study. The DMC responsibilities, authorities, and procedures will be documented in a separate DMC charter.

4. SUBJECT AND TREATMENT INFORMATION

The number of subjects in each analysis set will be summarized and listed by treatment group and overall. In addition, the distribution of subject enrollment by region, country, and site ID will be presented unless otherwise noted.

4.1. Demographics and Baseline Characteristics

Table 2 presents a list of the demographic variables that will be summarized by treatment group and overall for the efficacy analysis set. Table 3 presents a list of the baseline characteristics variables that will be summarized by treatment group and overall for the efficacy analysis set.

Table 2: Demographic Variables

Continuous Variables:	**Summary Type**
Age (years)	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum]).
Weight (kg)	
Height (cm)	
Systolic Blood Pressure/Diastolic Blood Pressure (SBP/DBP (mmHg)	
Categorical Variables	
Age (<65 years, ≥65 years)	Frequency distribution with the number and percentage of subjects in each category.
Sex (male, female, undifferentiated)	
Race[a] (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, White, Other, Multiple)	
Ethnicity (Hispanic or Latino, not Hispanic or Latino)	
Geographical Region (North America, Europe)	

[a] If multiple race categories are indicated, the race is recorded as 'Multiple'.

Table 3: Baseline Characteristics

Continuous Variables:	**Summary Type**
Time from initial diagnosis to randomization (months)	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum]).
Hematology	
Hemoglobin	
White Blood Cell Count (WBC)	
Platelet Count	
Absolute Neutrophil Count (ANC)	
Absolute Lymphocyte Count (ALC)	
Chemistry	
Creatinine	
Lactate Dehydrogenase (LDH)	
Uric Acid	
Alkaline Phosphatase	
Aspartate Aminotransferase (AST)	
Alanine Aminotransferase (ALT)	
Total Bilirubin	
Sodium	
Potassium	
Calcium	
Phosphate	
Categorical Variables	Frequency distribution with the number and percentage of subjects in each category.
Diagnosis (CLL, SLL)	
Rai Stage for CLL (0-II, III-IV)	
Binet Stage for CLL (A, B, C)	
Ann Arbor Stage for SLL (I, II, III, IIIE, IV)	
ECOG Performance Status (0, 1-2)	
CIRS total score (≤6, >6)	
Bulky Disease (Yes (LDi ≥5 cm), No (LDi <5 cm)	
Cytopenia (Yes, No)	
Anemia (Yes, No)	
Thrombocytopenia (Yes, No)	
Neutropenia (Yes, No)	
del11q (Yes, No)	
IGHV (mutated, unmutated, unavailable)	
High risk population (Yes, No)	

Elevated LDH (Yes (> ULN), No (≤ ULN))	
Serum β2 –microglobulin (≤3.5 mg/L, > 3.5 mg/L)	

4.2. Disposition Information

Disposition information will be summarized for the ITT population. The number of subjects undergoing, discontinuing and completing the study treatment as well as their reasons for treatment discontinuation will be summarized. Disposition due to COVID-19 will also be summarized and listed.

Descriptive statistics will be provided for time on study. Time on study is defined in a similar way as overall survival (OS) with reversed censoring, i.e., subject who died will be censored. Based on this definition, time on study is the same as length of follow up. The Kaplan-Meier method will be used to estimate the median time on study.

4.3. Treatment Compliance

Study agent compliance will be summarized descriptively, and will be calculated as follows:

- Ibrutinib or Venetoclax or Chlorambucil compliance (%) = (total dose actually taken / total dose prescribed) × 100%.
- Obinutuzumab compliance (%) = (actual dose of IV infusion on dosing schedule of six cycles) / (prescribed dose of IV infusion on dosing schedule of six cycles) × 100%.

4.4. Extent of Exposure

The number and percentage of subjects who receive study agent will be summarized by treatment group. Descriptive statistics for study agent duration (N, mean, SD, median, and range (minimum, maximum)) will be presented by treatment group for the safety analysis set. Study agent duration is defined as (date of last dose – date of first dose of study agent) + 1.

The number (%) of subjects with a dose modification (reduction and/or interruption [Ibr/Ven] and/or dose skip [Ob/Clb]) will be summarized. Reasons for dose modifications will also be summarized. For each subject, use the highest level of dose reduction to summarize categories – "One dose reduction" and "Two dose reductions", etc. The average daily dose of ibrutinib and venetoclax is calculated as (sum of total daily dose during the treatment phase) / study agent duration. The average daily dose of discrete dosing of Clb+Ob is calculated as (sum of total dose during the treatment phase) / total dosing days within study agent duration. The individual drugs that make up study treatment will be summarized separately. For the treatment phase, dosing information including relative dose intensity and dose intensity per protocol specified treatment will be summarized. Relative dose intensity is defined as

$$\frac{average\ daily\ dose}{planned\ dose\ intensity\ per\ protocol},$$

and dose intensity per protocol specified treatment is defined as:

$$\frac{Sum\ of\ actual\ dose\ administered}{planned\ total\ cumulative\ dose\ for\ the\ regimen\ per\ protocol}.$$

4.5. Protocol Deviations

Subjects with eligibility and other major protocol deviations will be listed by treatment group.

Protocol deviations will be based on clinical review of, but not limited to, the following aspects: (1) eligibility criteria, (2) patient safety, (3) efficacy assessment deviation, (4) treatment compliance. Protocol deviations will be closely monitored during the execution of the study and the final set of protocol deviation criteria will be finalized before database lock.

Major protocol deviations due to COVID-19 will be summarized and listed by treatment group. Listing of minor protocol deviations due to COVID-19 will also be provided. Summary table and listing of study assessment compliance will be presented.

4.6. Prior and Concomitant Medications

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO-DD). Prior medications are defined as any therapy used before the day of first dose (partial or complete) of study agent. Concomitant medications are defined as any therapy used on or after the same day as the first dose of study agent, including those that started before and continued on after the first dose of study agent, through the date of last dose of study drug. Using this definition, a medication can be classified as both prior and concomitant.

Summaries of prior and concomitant medications will be presented by Anatomical Therapeutic Chemical (ATC) class and drug generic term. The proportion of subjects who receive each concomitant medication will be summarized as well as the proportion of subjects who receive at least one concomitant medication. Concomitant medications of special interest will be provided: CYP3A inhibitors and inducers, hematologic growth factors, blood product transfusions, anticoagulation and anti-platelet agents.

5. EFFICACY

Analysis of efficacy endpoints will be conducted on the ITT population, unless specified otherwise. The analyses on PROs are detailed in Section 8.

5.1. Analysis Specifications

5.1.1. Level of Significance

All statistical tests will be performed at a 2-sided significance level of 5%, unless otherwise specified. All interval estimation will be reported using 2-sided 95% confidence intervals (CIs).

Multiplicity incurred from testing primary and secondary endpoints will be controlled using the serial gatekeeping procedure [6]. The hypothesis for a secondary endpoint will be tested if and

only if the null hypotheses for the primary endpoint and for the preceding secondary endpoints are rejected. The hierarchical order of secondary endpoint for testing is specified as follows:

- MRD negativity rate in bone marrow
- CR
- ORR
- OS
- Rate of sustained platelet improvement
- Rate of sustained hemoglobin improvement
- Time to improvement in FACIT fatigue score

5.1.2. Data Handling Rules

Unless specified otherwise, missing values will not be imputed.

5.2. Primary Efficacy Endpoint

5.2.1. Progression Free Survival based on Independent Review Committee

Progression-free survival (PFS) is defined as the time between the date of randomization and the date of disease progression, as assessed by the independent review committee (IRC), or date of death due to any cause, whichever occurs first, regardless of the use of subsequent anti-cancer therapy prior to documented PD or death.

All disease progression or death documented in the study will be considered as events, including those that occur after subsequent anti-cancer therapy is started or study medication is discontinued. Subjects who are progression free and alive will be censored at the date of last disease assessment. Subjects with no baseline or any post-baseline disease assessment will be censored at the date of randomization.

5.2.2. Estimand

Primary Trial Objective: To demonstrate the superiority of Ibr+Ven to that of Clb+Ob, in terms of progression-free survival (PFS) in subjects with CLL/SLL who are treatment-naïve.

Estimand Scientific Question of Interest: What is the effect on PFS of assigning subjects to Ibr+Ven vs. Clb+Ob?

This primary estimand is the main clinical quantity of interest to be estimated in this study, which is defined by the following five attributes [4]:

- Population: subjects with CLL/SLL who are treatment naïve
- Treatment: fixed duration Ibr+Ven vs. Clb+Ob
- Variable: PFS (PD is based on IRC assessment)

- Population-level summary: Kaplan-Meier estimates of PFS, hazard ratio of Ibr+Ven vs. Clb+Ob
- Intercurrent events and handling strategies: treatment discontinuation, use of subsequent anticancer therapy, death due to COVID-19

Intercurrent Events	**Name of Strategy for Addressing Intercurrent Events and Its Description**
Treatment discontinuation (due to AE or other reasons other than AE or worsening of disease)	**Treatment policy strategy:** use time to PD or death, regardless of whether or not treatment discontinuation had occurred.
Use of subsequent anticancer therapy	**Treatment policy strategy:** use time to PD or death, regardless of whether or not used subsequent anti-cancer therapy. **Hypothetical strategy:** subjects are censored at the last disease assessment showing no evidence of PD before the use of subsequent anti-cancer therapy.
Death due to COVID-19	**Composite variable strategy:** consider (pre-PD) death as a PFS event. **Hypothetical strategy:** subjects are censored at the last disease assessment before (pre-PD) death due to COVID-19.

5.2.3. Analysis Methods

5.2.3.1. Primary Analysis

- Assumptions:
  - Non-informative censoring assumed for all types of censoring.
  - Distinct baseline hazard for each stratum, common proportional hazard ratio across strata.
- Primary Estimator:
  - A stratified Cox regression model with study intervention as the sole explanatory variable will be performed, with stratification factors of IGHV gene mutational status and presence of del11q.
  - Hazard ratio and its 95% CIs will be estimated.
  - The treatment policy strategy is adopted for handling the intercurrent events of treatment discontinuation, use of subsequent anti-cancer therapy and the composite variable strategy is adopted for handling the intercurrent events of pre-PD death (PFS event) due to COVID-19.

Decision making will be based on the stratified log-rank test for statistical significance. Kaplan-Meier method will be used to estimate the distribution of PFS for each treatment group. The non-stratified Cox regression model may be used to analyze treatment effect on PFS after adjusting for covariates (selected demographics and baseline characteristics) as appropriate.

5.2.3.2. Sensitivity and Supplementary Analyses

Sensitivity Analysis of homogeneous baseline hazard:

- Assumptions:
  - Non-informative censoring assumed for all types of censoring.
  - Identical baseline hazard for each stratum and common proportional hazard ratio across strata.
- Sensitivity Estimator:
  - A unstratified Cox regression model with study intervention as the sole explanatory variable will be performed.

Sensitivity Analysis of disease assessment follow up:

- Assumptions:
  - Non-informative censoring assumed for all types of censoring.
- Sensitivity Estimator:
  - A stratified Cox regression model with study intervention as the sole explanatory variable will be performed, subjects will be censored at the last disease assessment if they progress or die after missing ≥2 consecutive planned disease assessment visits.

Supplementary Analysis of Estimand 2:

- Estimand 2 is defined to support the primary estimand. The only attribute that changes from the definition of the primary estimand is how the handling strategy is adopted for the use of subsequent anti-cancer therapies.
- Estimand 2:
  - Hypothetical strategy: if all subjects had continued treatment as planned and had not used any subsequent anti-cancer therapies.
  - Under the estimand 2, time to PD or death will be censored at the last disease assessment showing no evidence of PD before the use of subsequent anti-cancer therapy. Same analyses described in primary estimator will be applied.

Supplementary Analysis of Estimand 3:

- Estimand 3 is defined to support the primary estimand. The only attribute that changes from the primary estimand is the definition of variable of PFS where PD is assessed by investigator.
- Estimand 3:
  - Handling strategy: same as primary estimand.
  - Under the estimand 3, same analyses described in primary estimator will be applied.
  - The concordance rate between the IRC-determined PD and investigator-determined PD will be evaluated. The number and percentage of PD events and non-PD cases determined by investigator and by IRC will be cross-tabulated.

Supplementary Analysis of Estimand 4:

- Estimand 4 is defined to support the primary estimand. The only attribute that changes from the definition of the primary estimand is how the handling strategy is adopted for the death due to COVID-19:
- Estimand 4:
  - Hypothetical strategy: if all subjects had continued treatment as planned and had not died from COVID-19.
  - Under the estimand 4, time to PD or death will be censored at the last disease assessment before pre-PD death due to COVID-19. Same analyses described in primary estimator will be applied, however, this supplementary analysis would only be conducted if subject (pre-PD) death due to COVID-19 is >5% of total PFS events.

5.2.3.3. Subgroup Analysis

Subgroup analysis will be performed for the selected variables (as listed in Section 2.4) to assess the consistency and robustness of the treatment benefit for PFS. The non-stratified log-rank test analysis method for PFS will be used for each of the subgroup analysis. Median PFS with 95% CI, and hazard ratio between the two treatment groups within each subgroup and their 95% CI will be calculated using non-stratified Cox regression model. Subgroup analysis will be presented graphically in a forest plot.

5.3. Key Secondary Endpoints

5.3.1. Minimal Residual Disease Negativity Rate

MRD negativity rate is defined as the proportion of subjects who achieve MRD-negative disease status (<1 CLL cell per 10,000 leukocytes). All randomized subjects will be included in this analysis, subjects with missing MRD data are considered MRD positive. The primary analysis is the MRD negativity rate in bone marrow as assessed by next-generation sequencing (NGS) on or prior to initiation of subsequent anti-cancer therapy (including subsequent single-agent ibrutinib).

Supplemental analyses will be performed for MRD negativity rate in peripheral blood, at certain time point, for a subset of subjects achieving CR/CRi per IRC assessment, and alternative method of flow cytometry:

- MRD negativity rates in peripheral blood
- MRD negativity rates at 3-month and 12-month post completion of treatment
- MRD negativity rates among subjects who achieved a best overall response of CR/CRi per IRC assessment
- MRD negativity rates among subjects who achieved an overall response of CR/CRi per IRC assessment at 3-month and 12-month post completion of treatment
- MRD negativity rates assessed by flow cytometry: first use all samples as provided by central lab; then use only data from samples that meet the following criteria: 1) sample age

within the established specimen stability window (≤ 5 days); 2) a minimum of 50% sample viability; 3) collection of ≥ 500,000 leukocyte events (or <500,000 leukocyte events and ≥ 50 CLL events).

The Cochran-Mantel-Haenszel (CMH) chi-square test adjusted for the stratification factors will be used to compare MRD negativity rate between treatment groups, chi-square test will be used for non-stratified tests, and the Fisher's exact test may be used if the rate in any treatment group is too small.

5.3.2. Overall Response Rate

Overall response rate (ORR) is defined as the proportion of subjects achieving a best overall response of either CR, CRi, nPR, or PR per iwCLL criteria as evaluated by IRC on or prior to initiation of subsequent anti-cancer therapy (including subsequent single-agent ibrutinib). Subjects with missing post-randomization data are considered non-responders.

Overall response rate will be estimated according to the crude proportion of confirmed responders (PR or better) based on the best overall response and will be summarized by treatment group. Overall response rate will be compared between treatment groups using the CMH chi-square test, adjusted for the stratification factors. Rate ratio and its associated 95% CI between treatment groups will be performed.

Subjects who achieved PR by all parameters with the exception of reduction in ALC are considered PR with lymphocytosis (PRL). The ORR including PRL (per IRC assessment) will be summarized.

For overall response rate based on investigators' assessment, same analysis methods used for IRC reported overall response will be used.

Duration of response (DoR) is defined as the interval between the date of initial documentation of a response including PR with lymphocytosis and the date of first documented evidence of progressive disease or death. The censoring rule for DoR is the same as PFS. Only subjects who achieved a PR or better will be included in the analysis of duration of response. Duration of response will be summarized descriptively using the Kaplan-Meier method and no inferential comparison will be made between treatment groups.

5.3.3. Complete Response Rate

Complete response (CR) rate is defined as the proportion of subjects who achieved CR or CRi on or prior to initiation of subsequent anticancer therapy (including subsequent single-agent ibrutinib). The rates will be compared using CMH chi-square test between treatment groups, adjusted for the stratification factors. Time to complete response will be analyzed for subjects with CR or CRi and is defined as the interval between the date of randomization and the date of initial documentation of a CR/CRi.

Duration of complete response (DoCR) is 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. Duration of complete response will be summarized descriptively using the Kaplan-Meier method and no inferential comparison will be made between treatment groups.

5.3.4. Sustained Hematologic Improvement

Sustained hematologic improvement is defined as hematological improvement that is sustained continuously for ≥56 days without blood transfusion or growth factors on or prior to initiation of subsequent anti-cancer therapy (including subsequent single-agent ibrutinib):

- Hemoglobin levels increase ≥2 g/dL from baseline and lasts for at least 56 days without blood transfusion or growth factors;
- Platelet counts increase ≥50% over baseline lasts for at least 56 days without blood transfusion or growth factors.

Proportions of subjects achieving sustained hemoglobin and platelet improvement will be summarized by treatment group, respectively. These proportions will be compared using the CMH chi-square test.

Supplemental analysis will be conducted similarly for subjects with cytopenia at baseline. The subjects without any post-baseline hematologic assessment will be considered as having no improvement.

5.3.5. Overall Survival

Overall survival (OS) is defined as the time from date of randomization to date of death from any cause. If the subject is alive or the vital status is unknown, the subject will be censored at the date the subject was last known to be alive. Death due to COVID-19 is considered as an intercurrent event, the composite variable strategy is adopted (i.e. consider death due to COVID-19 as an OS event) in the primary analysis of OS. If number of subject deaths due to COVID-19 is >5% of total OS events, then the hypothetical strategy is adopted (censoring at the date of death due to COVID-19) as a supplementary analysis.

Overall survival will be analyzed using the similar analysis methods as used for primary analysis of PFS (Section 5.2.3), except for the use of un-stratified log-rank test and un-stratified Cox regression model if number of event is less than 10% of ITT analysis set.

5.4. Other Efficacy Variables

5.4.1. Time to Next Treatment

Time-to-next treatment is measured from the date of randomization to the start date of any subsequent anti-cancer therapy including single-agent ibrutinib as per protocol. Subjects without subsequent therapy will be censored at the last known alive date. Time-to-next treatment will be analyzed using the same analysis methods as that for PFS.

Number of subjects with subsequent anti-cancer therapy will be summarized by therapy type. Listing of subjects with subsequent anti-cancer therapy will also be provided.

5.4.2. Tumor Lysis Syndrome (TLS) risk reduction

TLS risk reduction for subjects in Ibr+Ven arm will be summarized. TLS risk reduction rate is the proportion of subjects with TLS risk reduced from high at baseline to medium or low after ibrutinib lead-in. Descriptive statistics will be provided. The proportion of subjects with hospitalization indicated due to TLS risk (i.e. subjects with high TLS risk and subjects with medium risk of TLS and creatinine clearance <80 mL/min) will also be summarized at baseline and after ibrutinib lead-in.

6. SAFETY

Safety will be analyzed using the incidence and severity of AEs, laboratory tests, and electrocardiogram (ECG) measurements. Unless specified otherwise, all safety analyses will be based on the safety analysis set, however, safety data from Subsequent Therapy Phase will be summarized separately. Descriptive statistics will be reported for all safety data. Inferential statistics are not planned to be performed on safety data. Summary table and listing for treatment-emergent COVID-19 adverse events will also be presented.

The baseline value for safety analysis is defined as the value collected at the time closest to and prior to the start of study medication. Unless otherwise stated, safety data will be summarized by actual treatment group.

6.1. Adverse Events

Adverse events will be summarized following Table 4.

Table 4. Summary of Adverse Event Analyses to be Performed

Category	Analysis	Sorted By	Cut off
General	Overall summary		
	TEAEs	SOC+ PT+ toxicity grade	All; 10%
	Serious TEAEs	SOC+ PT + toxicity grade	All; 2%
	Grade 3 or higher TEAEs	SOC+ PT+ toxicity grade	All; 2%
	Drug-related TEAEs	SOC+ PT+ toxicity grade	All; 5%
	TEAEs leading to death	SOC+ PT	
	TEAEs leading to dose reduction	SOC+ PT	
	TEAEs leading to dose interruption	SOC+ PT	
	TEAEs leading to drug discontinuation	SOC+ PT	
	AEs of clinical interest (Hemorrhagic events)	PT + toxicity grade	
	Other safety observations (e.g. other malignancies)	PT + toxicity grade	
	Deaths within treatment-emergent period	Reason for death	

Category	Analysis	Sorted By	Cut off
Subgroup	Overall summary		
	TEAEs	SOC+ PT+ toxicity grade	

6.1.1 All Adverse Events

The verbatim terms used in the CRF by investigators to identify AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). These coded AE terms are referred to as preferred terms (PT); classification into System Organ Class (SOC) is a result of the coding process.

The treatment-emergent period is defined as the time from first dose date through 30 days after last dose date, or the day before subsequent anti-cancer therapy (including subsequent single-agent ibrutinib), whichever occurs first. Treatment-emergent AEs (TEAEs) are defined as one or more of 1) those that occur in treatment-emergent period; 2) present before first dose but worsened in toxicity grade during treatment; 3) had missing start date and its end date is during the treatment; or 4) was a drug-related event. Drug-related AEs are those assessed by investigator as being possibly, probably or very likely related to study drug. To determine TEAEs, partially missing AE start dates will be imputed according to the rules stated in Section 2.7.

For each TEAE, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized. Tables will be sorted by frequency in incidence (the highest to lowest incidence).

For subjects using CYP3A inhibitor during treatment-emergent period, all TEAEs will be summarized by SOC, PT, maximum severity, strong/moderate CYP3A inhibitor (Yes vs No), and strong CYP3A inhibitor (Yes vs No).

6.1.2 Adverse Events of Clinical Interest and Other Safety Observations

AEs of clinical interest and other safety observations (e.g. other malignancies) will be summarized by treatment group.

Hemorrhagic events will be identified by hemorrhage Standardized MedDRA Query (SMQ) excluding laboratory terms and be tabulated. Major hemorrhage is a subset of hemorrhagic events which are grade ≥ 3 or serious or belong to central nervous system (CNS) hemorrhage/hematoma.

Other malignancies are defined as new malignant tumors including solid tumors, skin malignancies and hematologic malignancies and are to be reported for the duration of study treatment and during any protocol-specified follow-up periods including post-progression follow-up for overall survival.

6.1.3 Deaths

A summary of the number of deaths during the treatment-emergent period will be provided, along with the primary cause of death. In particular, frequencies of deaths due to study treatment-related

adverse events will also be reported. A death is study medication-related death if the primary cause is a drug related AE. Death during the entire study period will also be summarized, as well as the primary cause.

6.2. Clinical Laboratory Tests

Laboratory data of hematology and serum chemistry up to 30 days after last dose or the day before subsequent anti-cancer therapy (including subsequent single-agent ibrutinib), whichever occurs first, will be reported in International System of Units (SI).

For hemoglobin, absolute neutrophil count (ANC), and platelets, toxicity will be assessed by the grading scale for hematologic toxicity in CLL studies in the iwCLL 2008 guidelines. Other laboratory results will be graded according to NCI-CTCAE version 4.03. Note that toxicity grading for creatinine increase will be based on the NCI CTCAE v4.03 criteria but limited only to the part based on the upper limit of normal (ULN), the other part, that is based on change from baseline, will not be used for toxicity grading. Generic normal ranges will be applied whenever reference ranges are not available.

The following laboratory tests will be analyzed:

- Hematology: hemoglobin, white blood cell (WBC), ANC, absolute lymphocyte count (ALC), and platelets
- Coagulation (screening only): Prothrombin international normalized ratio (INR), activated partial thromboplastin time (aPTT)
- Chemistry: alkaline phosphatase, ALT, AST, bilirubin (total), creatinine, creatinine clearance (CrCl), LDH, potassium, sodium, calcium, phosphorus, and uric acid

Descriptive statistics (mean, standard deviation, median and range) will be calculated for the raw data and for their changes from baseline at each time point of assessment. Parameters will be summarized by toxicity grade. Change from baseline to the worst grade during the treatment will be provided as shift tables for selected parameters. In addition, treatment-emergent worsening in toxicity grade will be summarized for selected hematology and chemistry parameters.

Liver function abnormality by Hy's Law: For subjects with any elevated AT (AST or ALT) of >3×ULN, ALP <2×ULN, and associated with an increase in bilirubin (total) ≥2×ULN occurred within 28 days of each other, a listing for all subjects with all such records will be provided and a summary table of the number of such subjects will be provided by treatment group.

The frequencies of abnormal treatment emergent uric acid will be summarized by treatment group.

Laboratory TLS per Howard criteria will also be summarized for Ibr+Ven arm.

6.2.1. Analysis of Lymphocytosis

For all subjects with baseline and any post-baseline ALC measurements, a summary of peak ALC values will be provided by treatment arm.

Lymphocytosis is defined as an elevation in ALC of ≥50% compared to baseline and to ≥5×10^9/L (5,000/μL) at a post-baseline assessment. The number of subjects with at least one occurrence of lymphocytosis will be summarized. For subjects with lymphocytosis, resolution of lymphocytosis is defined as 1) a decrease of ALC value to the baseline level or lower, or 2) an achievement of ALC value that is below 5×10^9/L (5,000/μL), whichever occurs first.

The following analyses will be conducted for subjects with lymphocytosis by treatment group:

- ALC at peak and time to peak ALC within the time period from the first dose of study drug to 9 months from start of study treatment (Study day 274), 30 days following the last dose of study drug or initiation of subsequent anti-cancer therapy (including subsequent single-agent ibrutinib), whichever occurs earliest.

- Time to lymphocytosis is defined as the time from first dose date of study treatment to the first post-baseline ALC which meets the lymphocytosis criteria and will be summarized descriptively for subjects who developed lymphocytosis.

- Duration of lymphocytosis is defined as the duration of time from the earliest date on which the ALC value met the lymphocytosis criteria at a post-baseline assessment to the earliest date on which a subsequent ALC value met the resolution criteria. Subjects who have developed lymphocytosis but not recovered will be censored at the last available ALC measurements at or prior to initiation of subsequent anti-cancer therapy (including subsequent single-agent ibrutinib).

6.3. Electrocardiogram

Clinically significant ECG abnormalities will be summarized and listed. Descriptive statistics will be calculated for the ECG parameters at baseline. All treatment-emergent abnormal findings will be tabulated, displaying the number of subjects with abnormal findings after dosing up to the end (Day 28) of the last cycle. An abnormal finding is considered to be treatment-emergent if it occurred during treatment and up to 30 days after the last dose.

7. SUBSEQUENT THERAPY PHASE WITH SINGLE-AGENT IBRUTINIB

Subjects who have IRC-confirmed disease progression and have active disease requiring treatment may be eligible to receive single-agent ibrutinib given until disease progression or unacceptable toxicity as part of the Subsequent Therapy Phase of this study. Participation in the Subsequent Therapy Phase is not mandatory and is based on the investigator´s decision. For subjects who receive at least one dose of subsequent single-agent ibrutinib as part of this study, their demographics and baseline characteristics, disposition information, and exposure of ibrutinib will be summarized or listed by their initial treatment arm. Baseline value is the last non-missing value collected on or before the administration of the first dose of subsequent ibrutinib. The reference date is defined as the date of first dose of subsequent ibrutinib for all data.

For efficacy data, a listing of response evaluations for subjects in Ibr+Ven arm will be performed.

Safety analysis including incidence of adverse events and death will also be presented. Treatment emergent period for subsequent ibrutinib therapy is defined as the time from the first dose date of subsequent ibrutinib therapy through 30 days after last dose date, or until the day before a second subsequent therapy, whichever occurs first.

8. PATIENT-REPORTED OUTCOMES

Patient-reported outcomes will be measured by three questionnaires: the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ)-C30, the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue scale, and the EuroQol 5 Dimension 5 Level questionnaire (EQ-5D-5L). Refer to the protocol for samples of PRO scales and data collection schedule.

8.1.1. EORTC QLQ-C30

EORTC QLQ-C30 includes 30 separate items resulting in 5 functional scales (physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning), 1 global health status scale, 3 symptom scales (fatigue, nausea and vomiting, and pain), and 6 single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). Scores will be derived using validated scoring algorithms according to EORTC QLQ-C30 Scoring Manual [1]. Scores range from 0 to 100 (for functional and global QoL scales, higher scores indicate a better level of functioning). EORTC QLQ-C30 improvement/worsening is defined as ≥10 points for each assessment post baseline.

8.1.2. EQ-5D-5L

The EQ-5D-5L consists of a 5-item descriptive system and the EuroQol visual analog scale (EQ-5D VAS) of self-rated health, with scores ranging from 0 (worst imaginable health state) to 100 (best imaginable health state). Responses for the 5 dimensions are combined into a 5-digit number describing a respondents' health state that can be converted into a single index value or utility score (using the United Kingdom weights), ranging from –1 to 1, where lower scores indicate a worse health status. A minimum difference of ≥0.07 points change in utility score is considered clinically important; for the VAS health rating, a minimum important difference is ≥7 points change.

8.1.3. FACIT-Fatigue

The FACIT-Fatigue Scale measures fatigue severity and impact on daily activities. It includes 13 items that assess tiredness, weakness and difficulty conducting usual activities due to fatigue. Scores range from 0 to 52 with high scores indicating less fatigue. FACIT improvement/worsening is defined as ≥3 points change for each assessment post-baseline.

8.1.4. Analysis Methods

Descriptive statistics (number of observations, mean, standard deviation, median, minimum, maximum) at baseline and each post-baseline time point will be reported by treatment group for

FACIT-Fatigue total score, each scale of EORTC QLQ-C30 and EQ 5D visual analogue scale and weighted utility score.

Compliance

Compliance rates defined as the number of questionnaires received as a percentage of the number expected per protocol-specified collection schedule are assessed for EORTC QLQ-C30, EQ-5D-5L and FACIT-Fatigue.

Mixed Model for Repeated Measures

For each of the PRO measures of interest, a mixed-effects model with repeated measures (MMRM) analysis is conducted estimating change from baseline at each time point. ITT subjects who have a baseline value and at least 1 post-baseline value are included in the analysis.

For each scale, change from baseline is fitted to a mixed-effects model including subjects as a random effect, and baseline value, treatment, time, treatment-by-time interaction, and randomization stratification factors as fixed effects.

Time to Improvement and Deterioration Analysis

Using a threshold value for improvement and deterioration specific to the PRO measures of interest, time to improvement and time to deterioration will be compared between treatment groups in ITT subjects. Subjects who have not experienced event at the time of analysis will be censored on the last known date without event. Subjects with no on-study assessment or no baseline assessment will be censored at date of randomization.

Distributions of time-to-event variables will be estimated using the Kaplan-Meier product-limit method. Median times to event with 2-sided 95% confidence intervals will be estimated. The stratified log-rank test accounting for stratification factors will be used for treatment comparison. A stratified Cox proportional-hazards model will provide estimates of hazard ratios with 95% confidence intervals.

Exploratory analyses with Patient-reported outcome Questionnaires

In addition to the planned analyses on the domains and scales from each of the patient-reported outcome questionnaires, exploratory analyses at the individual item level will be conducted to better understand domains that show significant effects or trends toward significance. In each case where an individual item analysis is conducted, the analytic approach will replicate that described for the scale and domain scores.

Analysis Visits

To determine the scheduled time points, all PRO scores are to be assigned to a particular time window for a scheduled time point based on the rules presented in Table 5. In the case that more than 1 score are found within a time window, the score closest to the window center will be used

in the analysis. In the case that there are 2 values that are equidistant from the center, the value prior to the center will be used.

Details for target date for each scheduled visit and time interval between scheduled visits are provided in the table below:

Table 5. Visit Windows for PRO Assessments

Analysis visit (cycle)	Week	Start (Day)	Target (Day)	End (Day)
Cycle 1 (Baseline)	0	-30	1	29
Cycle 3	8	30	57	85
Cycle 5	16	86	113	141
DE 2	24	142	169	211
DE 3	36	212	253	295
DE 4	48	296	337	379
DE 5	60	380	421	463
DE 6	72	464	505	561
DE 7	88	562	617	673
DE 8	104	674	729	785
DE 9	120	786	841	897
DE 10	136	898	953	1009
DE 11	152	1010	1065	1121
DE 12	176	1178	1233	1317
DE 13	200	1318	1401	1485
DE 14	224	1486	1569	1653
… …	… …	… …	… …	… …
Post-PD Follow-up 1	NA	PD date + 84	PD date + 168	PD date + 251
Post-PD Follow-up 2	NA	PD date + 252	PD date + 336	PD date + 419

Each cycle is 28 days.

In addition, the PROs for end-of-treatment (EOT) Visit is within 30 days (+7) after last dose of study medication.

After disease progression, ePRO assessment will be limited to the EQ-5D-5L questionnaire only for the first 2 Post-PD Visits.

9. PHARMACOKINETICS

All concentrations below the lowest quantifiable concentration or missing data will be labeled as such in the concentration database. Concentrations below the lowest quantifiable concentration will be treated as zero in the summary statistics. The number of subjects and samples excluded from the analysis will be clearly documented in the Clinical Study Report. Descriptive statistics will be used to summarize ibrutinib, PCI-45227, and venetoclax plasma concentrations at each sampling time point. Ibrutinib and PCI-45227 trough levels in presence and absence of venetoclax will be compared graphically, if appropriate.

10. BIOMARKER ANALYSIS

Details of analysis plan for other biomarkers and their results will be presented in a separate report.

11. CHANGES TO PROTOCOL-SPECIFIED ANALYSES

The following analyses are different from those described in the protocol:

- Additional supplementary/sensitivity analyses to mitigate the impact of the COVID-19 are added.
- Time to next treatment is changed to be an exploratory endpoint, instead of a key secondary endpoint.
- NGS is used as the primary method for MRD analyses, MRD by flow cytometry is used for supplementary analyses.
- The definition for TLS risk category is updated to the following per Venetoclax USPI for CLL [5]:
    - Low: all lymph node < 5cm AND ALC < $25x10^9$/L
    - Medium: any lymph node 5cm to < 10cm OR ALC ≥ $25x10^9$/L
    - High: any lymph node ≥ 10cm OR ALC ≥ $25x10^9$/L AND any lymph node ≥ 5cm

Other changes include:

- The abbreviations used for treatment arm and comparator arm are changed to “Ibr+Ven” and “Clb+Ob”, respectively.
- The term “MRD-negative remission” is replaced by the phrase “MRD negativity”.

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