Janssen Research & Development *

Clinical Protocol

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
Amendment 4

JNJ-54179060 (ibrutinib)

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GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

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PROTOCOL AMENDMENTS

Protocol Version	Date
Original Protocol	12 January 2018
Amendment 1	6 June 2018
Amendment 2	22 January 2019
Amendment 3	12 August 2019
Amendment 4	19 December 2019

Amendments below are listed beginning with the most recent amendment.

Amendment 4 (19 December 2019)

The overall reasons for the amendment: To update safety information to align with the ibrutinib Investigator's Brochure (IB) to include information regarding cerebrovascular accidents as a new safety observation identified from the post-marketing setting, and to clarify that assessment of pulse/heart rate and blood pressure is expected at every protocol-specified visit.

Applicable Section(s)	Description of Change(s)
Rationale: To update the safety for ibrutinib, including information on cerebrovascular accidents.	
Attachment 1, Ibrutinib Risks	Safety information on ibrutinib updated to align with the current IB.
Rationale: To clarify that regular monitoring of pulse/heart rate and blood pressure is expected at every protocol-specified visit.	
Table 1, Table 2, Table 3, and Table 4 (Time and Events Schedules); 9.5 Safety Evaluations	Additional pulse/heart rate and blood pressure assessments added. Footnotes added to clarify that pulse/heart rate and blood pressure should be recorded in source documents but will not be routinely collected in the eCRF. Vital signs description updated to specify pulse/heart rate and blood pressure evaluation is expected at every visit, and guidelines on monitoring and management of cardiovascular toxicities was added. In addition, ECG text was updated to clarify the timing for assessment and optimal monitoring and management of cardiovascular toxicities (consider consultation with a cardiologist).
Rationale: To clarify the baseline evaluations to be conducted for those subjects who receive subsequent therapy with single-agent ibrutinib.	
Table 4 (Time and Events Schedule)	The following baseline evaluations were added: medical history, CIRS score, ECOG PS, ECG, vitals, weight, and hepatitis testing. A clarifying footnote (footnote c) was added to specify that only new medical conditions since the initial screening period or medical conditions that have worsened since baseline should be captured in the case report form and CIRS only needs to be re-evaluated if new or worsening medical conditions are reported.
Rationale: To clarify that annual CT imaging during subsequent therapy with single-agent ibrutinib should coincide with disease evaluation visits.	
Table 4 (Time and Events Schedule; footnote g)	CT imaging is expected for subjects who were initially treated with I+VEN (Treatment Arm A); this will occur at the following timepoints: baseline, Week 16, Week 48, and annually thereafter coinciding with the DE visits until progression.

Applicable Section(s)	Description of Change(s)
Rationale: To clarify that subjects in Treatment Arm B remain eligible for subsequent therapy with single-agent ibrutinib even if they do not complete open-label therapy because this would not be expected to affect response and tolerability to ibrutinib.	
Synopsis (Overview of Study Design); Figure 2; Section 3.1 Overview of Study Design; Section 3.2 Study Design Rationale; 9.1.5.1 Eligibility for the Subsequent Therapy Phase	Removed text specifying that treatment with I+VEN or G-Clb needs to be completed to be eligible for subsequent therapy with single-agent ibrutinib. Figure 2 bullet on "completed study treatment" updated to specify that this pertains to Arm A. The text was updated to clarify that subjects randomized to Treatment Arm B may remain eligible for subsequent therapy even if the protocol-specified treatment is not completed.
Rationale: To clarify that serum chemistry and hematology assessments may be done outside of the treating institution for non-cycle visits.	
Table 4 (Time and Events Schedule; footnote e)	Footnote "e" added to clarify that testing may be done outside of the treating institution for non-cycle visits.
Rationale: To clarify that medical history needs to be reviewed as complete before a subject is considered eligible to receive subsequent therapy with single-agent ibrutinib.	
9.1.5 Subsequent Therapy Phase	Added that eligibility review should include review that medical history is complete.
Rationale: To remove specificity that a stratified analysis will be done for overall survival because the number of events may be too small in some of the strata.	
11.4 Efficacy Analyses; 11.4.2 Secondary Endpoints	Deleted term "stratified" when describing the overall survival analysis. The details will be specified in the final Statistical Analysis Plan.
Rationale: To add an external link for examples of CYP3A inhibitors and inducers.	
Attachment 5	Inserted an additional link to FDA classification of CYP3A inhibitors and inducers.
Rationale: Throughout the protocol, minor grammatical, formatting, or spelling changes were made as needed.	

Amendment 3 (12 August 2019)

The overall reason for the amendment: The primary reason for the amendment is to add a Subsequent Therapy Phase in which eligible subjects who progressed after completing the Treatment Phase with either ibrutinib plus venetoclax (I+VEN; Treatment Arm A) or obinutuzumab plus chlorambucil (G-Clb; Treatment Arm B) can receive single-agent ibrutinib. Response data, as well as biomarker samples, will be collected to evaluate the efficacy of subsequent single-agent ibrutinib therapy in subjects previously treated with a fixed-duration of I+VEN.

Applicable Section(s)	Description of Change(s)
Rationale: A Subsequent Therapy Phase was added in which eligible subjects will be treated continuously with single-agent ibrutinib.	

Synopsis Overview of Study Design; 3.1 Overview of Study Design; 5 Treatment Allocation; 9.1.1 Overview; 9.1.3 Open-label Treatment Phase; 9.1.4 Follow-up Phase; 9.1.5 Subsequent Therapy Phase (new section); 9.2 Efficacy; 9.2.1.1 Radiographic Imaging Assessments; 9.2.1.3 Bone Marrow Assessments; 9.3.1 Pharmacokinetic Evaluations; 9.5 Safety Evaluations	Added description of the Subsequent Therapy Phase, including clarification of study evaluations and added clarifying text to description of Treatment Phase where appropriate
Table 4 Time and Events Schedule for Subsequent Therapy with Single-agent Ibrutinib (new table); Figure 2 Disease Evaluation and Treatment Schedule for Subsequent Therapy with Single-agent Ibrutinib (new figure)	Added the time and events schedule and schema for the Subsequent Therapy Phase
Synopsis Dosage and Administration; 6 Dosage and Administration; 6.3 Subsequent Therapy with Single-agent Ibrutinib (new section)	Added description of treatment to be administered in the Subsequent Therapy Phase
8 Concomitant Therapy	Clarified that concomitant therapy should be recorded during both the Treatment Phase and the Subsequent Therapy Phase
12.3.1 All Adverse Events	Clarified that AEs should be collected during the Subsequent Therapy Phase
1.6 Overall Rationale for the Study; 3.2 Study Design Rationale; 16.1 Study-specific Design Considerations	Added rationale for the Subsequent Therapy Phase
Rationale: Eligibility criteria for the Subsequent Therapy Phase was added.	
4. Subject Population; 9.1.5.1 Eligibility for the Subsequent Therapy Phase (new section)	Defined eligibility criteria for the Subsequent Therapy Phase and added a reference to this where overall study eligibility criteria are stated (Section 4).

3.1 Overview of Study Design	Added statements that eligible subjects for the Subsequent Therapy Phase must have completed the treatment with I+VEN or G-Clb and subsequently develop progressive disease (as confirmed by the Independent Review Committee [IRC]) that requires treatment per International Workshop on Chronic Lymphocytic Leukemia [iwCLL] criteria)
Rationale: Clarification of response categories to be used for the Subsequent Therapy Phase was added.	
9.2.3 Response Categories	Clarified that responses will be based on assessment by the investigator during the Subsequent Therapy Phase. Noted that confirmation of responses by the IRC may be pursued by the sponsor for regulatory purposes.
Rationale: Evaluations, exploratory objective, and exploratory endpoints associated with the Subsequent Therapy Phase were added.	
11.4.4 Subsequent Therapy Evaluations	Evaluations and exploratory endpoints for the Subsequent Therapy Phase were added.
Rationale: Clarified the purpose of the bone marrow aspirate and biopsy	
Table 3 Time and Events Schedule for Treatment and Post-Treatment Disease Evaluations Prior to Disease Progression Treatment Arm A and Treatment Arm B	Added the following text to Footnote d to aligned with Section 9.2.1.3: The bone marrow aspirate and biopsy should be sent to a local laboratory for standard evaluation and response assessment.
Rationale: Added a sample for biomarker assessment at DE8	
Table 3 Time and Events Schedule for Treatment and Post-Treatment Disease Evaluations Prior to Disease Progression Treatment Arm A and Treatment Arm B	Added a sample for biomarker assessment at DE8 and associated footnote f.
16.1 Study-specific Design Considerations	Added maximum total volume of blood collected in the Subsequent Therapy Phase Updated total volume of blood to be collected after the treatment period
Rationale: Minor errors were noted.	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made, and minor corrections and alignments among sections were incorporated.
15 Study-specific Materials	Removed the reference to IWRS codes since this is not a blinded study.
REFERENCES	Removed references that are no longer applicable.

Amendment 2 (22 January 2019)

The overall reason for the amendment: The primary reason for the amendment is to revise the duration of treatment in the I+VEN treatment arm of the trial based on available Phase 2 data with this combination.

Applicable Section(s)	Description of Change(s)
Rationale: The protocol has been adapted to reflect recent scientific insights from relevant Phase 2 studies indicating that the removal of the last 3 cycles (cycles 16, 17, and 18) of ibrutinib monotherapy is appropriate.	
Synopsis: Dosage and Administration	Update of data from relevant Phase 2 studies in which I+VEN has been investigated for the treatment of CLL.
Table 1 Time and Events Schedule for Treatment Arm A; Table 2 Time and Events Schedule for Treatment Arm B; and Table 3 Time and Events Schedule for Treatment and Post-Treatment Disease Evaluations Prior to Disease Progression Arm A and B	For Treatment Arm A, removal of 3 additional cycles of ibrutinib monotherapy following completion of combination therapy (I+VEN) in relevant Time and Events Schedules, study overview figure, and text. Adjustment of weeks on which Disease Evaluation visits with computed tomography (CT) imaging will occur as a result of the removal of 3 additional cycles of ibrutinib monotherapy following completion of combination therapy (I+VEN), including clarification of when hematology laboratory assessments are to be performed.
Figure 1 Disease Evaluation and Treatment Schedule	Update of blood volume to be collected for subjects assigned to Treatment Arm A commensurate with the reduction in treatment cycles.
1.5 Ibrutinib in Combination with Venetoclax in CLL	Clarification of procedure to collect samples for biomarker analysis.
1.6 Overall Rationale for the Study	
3.1 Overview of Study Design	
6.1 Treatment Arm A (Ibrutinib and Venetoclax) Administration	
9.1.3 Open-Label Treatment Phase	
9.2.1.3 Bone Marrow Assessments	
9.2.2 Minimal Residual Disease Assessments	
16.1 Study-Specific Design Considerations	
REFERENCES	
Rationale: The protocol was updated to inform of additional effort to evaluate ibrutinib monotherapy as subsequent therapy for subjects who were initially exposed to and progressed on I+VEN combination therapy.	
1.6 Overall Rationale for the Study	Language was included to inform of the possibility of enrolling subjects who relapsed or progressed after I+VEN therapy in this study in a clinical trial investigating the effectiveness of retreatment with ibrutinib.
Rationale: Minor revisions requested by a regulatory authority regarding concomitant medications were incorporated.	
8.2 Medications to be Used with Caution	Clarification of the concomitant use of CYP3A4 inhibitors with ibrutinib and venetoclax.

Rationale: The 18-month landmark was removed to avoid confusion on multiple minimal residual disease (MRD) analyses.	
11.4.2 Secondary Endpoints	The following statement was removed from the first secondary endpoint: Subjects without MRD measurement during the 18 months will be considered as MRD positive.
Rationale: Minor corrections and errors were addressed.	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made, and minor corrections and alignments among sections were incorporated.

Amendment 1 (6 June 2018)

The overall reason for the amendment: The overall reason for the amendment is to address Health Authority feedback and to update protocol based on early pharmacokinetic (PK) results from ongoing Phase 2 study of I+VEN.

Applicable Section(s)	Description of Change(s)
Rationale: Changes have been made to the protocol to address Health Authority feedback.	
Table 1 Time and Events Schedule for Treatment Arm A, footnote "h"; Table 2 Time and Events Schedule for Treatment Arm B, footnote "h"	Footnote added to specify that pregnancy testing must be done or repeated within 7 days before the first dose of study treatment.
8.2 Medications to be Used With Caution; 8.3 Prohibited Concomitant Medications	Text regarding prohibited use of strong CYP3A inhibitors during venetoclax administration was moved from Section 8.2 to Section 8.3 and a cross reference to Section 8.3 was added.
8.3 Prohibited Concomitant Medications	Text was added to specify that live vaccines must not be administered during study treatment phase.
12.1.1 Adverse Event Definitions and Classifications	Text regarding expectedness of adverse events (AEs) was revised for clarity.
12.3.1 All Adverse Events	Text was revised to clarify requirements for reporting of progression of disease.
Rationale: Based on early PK results from ongoing Phase 2 study of I+VEN, preliminary data, venetoclax PK sampling, and new dosing guidance were added to protocol.	
Table 1 Time and Events Schedule for Treatment Arm A, Laboratory Assessments	New row added for collection of predose venetoclax PK samples in Cycles 5 and 6 only.
1.5 Ibrutinib in Combination With Venetoclax in CLL	Added summary of preliminary data from a Phase 2 study of I+VEN regarding venetoclax and ibrutinib exposures.
Synopsis – Secondary Objectives; 2.1 Objectives and Endpoints	Secondary PK objective and endpoint were modified to account for venetoclax PK analysis.
6.1.1.2 Ibrutinib Dose Modification; 6.1.2.3 Venetoclax Dose Modification	Text revised to clarify that if an AEs is considered potentially related to both drugs for subjects in Treatment Arm A, the recommended first action should be venetoclax dose modification before ibrutinib dose modification.

9.3 Pharmacokinetics; 9.3.1 Pharmacokinetic Evaluations; 9.3.2 Pharmacokinetic Analytical Procedures	Text added to specify that blood samples will be collected for PK analysis of venetoclax.
9.3.3 Pharmacokinetic Parameters	Text added to specify that PCI-45227 and venetoclax $C_{trough,ss}$ data will be summarized by descriptive statistics. Text regarding PK analyses moved to Section 11.5.
11.5 Pharmacokinetic Analyses	Text added to specify that venetoclax PK data will be summarized by descriptive statistics and to describe ibrutinib and PCI-45227 analyses.
Rationale: According to the Chlorambucil Summary of Product Characteristics, patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medication.	
4.2 Exclusion Criteria	New exclusion criterion 23 added excluding subjects with galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption from study enrollment.
Rationale: To align with product labels for study treatments with respect to hypersensitivity to active substances or excipients.	
4.2 Exclusion Criteria	New exclusion criterion 24 added excluding subjects with any contraindication to one of the study medications including hypersensitivity to the active substance or to any of the excipients of ibrutinib, venetoclax, obinutuzumab, or chlorambucil.
Rationale: To rectify missing biomarker data points.	
Table 1 Time and Events Schedule for Treatment Arm A, Laboratory Assessments	Cycle 4 Day 15 biomarker sampling added.
Table 2 Time and Events Schedule for Treatment Arm B, Laboratory Assessments, footnote “i”	Cycle 4 Day 15 biomarker sampling added. Footnote added to clarify that biomarker sample will be collected on subjects who are coming to Clinic for on-site chlorambucil administration on Cycle 4 Day 15.
9.4 Biomarkers	Text added to specify that samples may be evaluated for cytogenetics.
Rationale: Additional PK and biomarker samples in Treatment Arm A and Treatment Arm B will be collected.	
16.1 Study-Specific Design Considerations	Blood volumes to be collected have been updated.
Rationale: Clarify the threshold by which the presence of a TP53 mutation is considered exclusionary.	
4.2 Exclusion Criteria; 9.1.2 Screening Phase; References	Text was added to specify that subjects with known presence of *TP53* mutations detected at a threshold of >10% variable allele frequency will be excluded from the study. New publication (Malcikova 2018) added to References and citation to this publication added.

Rationale: Text was updated to align with the global protocol template.	
16.2.5 Long-Term Retention of Samples for Additional Future Research	Sample storage retention was revised to from 2 years to 15 years after end of study.
Rationale: Additional references regarding CLL diagnosis are available.	
4.1 Inclusion Criteria; References	New publication (Rawstron 2018) added to References and citation to this publication added.
Rationale: Revisions and modifications were made throughout the protocol to increase clarity, for consistency within this protocol, or to correct omissions and errors.	
Synopsis – Subject Population	Bold text was added: Subjects with deletion of the short arm of chromosome 17 (del17p) **or known *TP53* mutations** are excluded.
Table 1 Time and Events Schedule for Treatment Arm A, Disease Evaluations; Table 2 Time and Events Schedule for Treatment Arm B, Disease Evaluations	Text was **revised** to specify that disease evaluations (DEs) will be performed every 12 weeks after randomization through Week ~~60~~ **84**, then every 16 weeks through Week ~~156~~ **164**
Table 1 Time and Events Schedule for Treatment Arm A, Laboratory Assessments	Cycle 4 column header "D21" corrected to "D22". An "X" was added for Hematology at Screening for consistency with Table 3. An "X" was added for Biomarker blood samples at Screening for consistency with Table 3.
Table 2 Time and Events Schedule for Treatment Arm B, Laboratory Assessments	An "X" was added for Biomarker blood samples at Screening for consistency with Table 3.
Table 3 Time and Events Schedule for Treatment and Post-Treatment Disease Evaluations Prior to Disease Progression Treatment Arm A and Treatment Arm B	For column "Weeks 84 through 164", Week 8 added to DE range.
1.3 Ibrutinib	Text added to specify that Pharmacyclics LLC is an AbbVie Company.
4.1 Inclusion Criteria; 4.2 Exclusion Criteria; References; Attachment 2 Cumulative Illness Rating Scale (CIRS)	New publication (Salvi 2008) added to References and Attachment and in-text cross references added. Link to publication added to Attachment.
5 Treatment Allocation	The randomization will be balanced by using ~~randomly~~ permuted block~~s~~ and will be stratified by immunoglobulin heavy-chain variable mutational status (mutated vs. unmutated vs. not available) and presence of del11q (yes vs. no).

6.1.1.2 Ibrutinib Dose Modification; 6.1.2.3 Venetoclax Dose Modification	Cross reference to Attachment 5 corrected to Attachment 9.
6.2 Treatment Arm B (Chlorambucil plus Obinutuzumab) Administration	Redundant text referring to chlorambucil and obinutuzumab product labels deleted.
6.2.1.2.1 Infusion Reactions	Cross reference to Attachment 8 corrected to Table 10.
8.3 Prohibited Concomitant Medications	Text was revised to specify that: • any non-study anti-leukemic therapy is prohibited until disease progression has occurred • corticosteroids at dosages equivalent to prednisone >20 mg/day for >14 days are prohibited until disease progression has occurred Text was added to align with existing content found in Attachment 9: warfarin or other vitamin K antagonists should not be administered concomitantly with ibrutinib.
9.1.1 Overview	Text was added to specify that repeat blood samples may be taken for technical issues.
9.2.1.2 Definition of Measurable and Assessable Disease	Text was added to clarify that measurable sites of disease are target lesions and lesions not included in the target lesion assessment should be considered as assessable (non-target) lesions. Text in strikethrough was removed: Investigators should provide a qualitative assessment ~~(ie, increased, decreased, normal, no change)~~ of the spleen and liver at screening and in all subsequent DE visits.
9.2.2 Minimal Residual Disease Assessments	Text was added to specify that the first draw of the bone marrow aspirate should be sent for central MRD analysis.
9.2.3 Response Categories, Table 12: Criteria for Response Categories	Text in strikethrough was removed: Footnote pertaining to partial response (PR) has been revised: PR: At least 2 criteria from Group A plus 1 of the criteria from Group B must be met. ~~In all cases, in order for a response to be termed a PR, the blood lymphocyte count should be normalized or decreased >50% from baseline (if elevated at baseline).~~
9.5 Safety Evaluations - Physical Examinations	Text in strikethrough was removed: The status ~~(increased, decreased, normal, absent)~~ of nodal lesions, the liver, and spleen must be reported at each DE visit.
14.1 Physical Description of Study Interventions; 14.2 Packaging; 14.4 Preparation, Handling, and Storage	Text revised regarding study treatment description, packaging, handling, and storage.
Attachment 9 Medications to be Used with Precaution with Ibrutinib and Venetoclax	Dose for ibrutinib dose reduction with moderate cytochrome p450 (CYP) inhibitor use revised.
Antiplatelet Agents and Anticoagulants - Ibrutinib	Text revised to remove redundant text and for clarity.
Attachment 10 CLL and SLL Staging Criteria	The Ann Arbor SLL Staging System with Cotswold's Modifications was added.

Rationale: Minor corrections and errors were addressed.

Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

SYNOPSIS

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)

OBJECTIVES AND HYPOTHESIS

Primary Objective

The primary objective of the study is to assess progression-free survival (PFS) from treatment with ibrutinib plus venetoclax (I+VEN) compared with obinutuzumab plus chlorambucil (G-Clb) as assessed by an Independent Review Committee (IRC).

Secondary Objectives

Key secondary objectives are to evaluate the following: rate of minimal residual disease (MRD)-negative remissions; overall response rate (ORR), including complete response (CR) rate, and response duration as assessed by an IRC; overall survival (OS); time-to-next treatment; trough levels of ibrutinib and venetoclax when given in combination; and safety.

Hypothesis

Treatment with the combination of I+VEN will result in longer PFS compared with G-Clb in subjects with previously untreated chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL).

OVERVIEW OF STUDY DESIGN

This is a randomized (1:1), open-label, multicenter, Phase 3 study to determine the efficacy and safety of the combination of I+VEN, compared with G-Clb, in approximately 200 subjects with previously untreated CLL/SLL who meet the International Workshop on CLL (iwCLL) treatment criteria. Randomization will be stratified by 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 with confirmed disease progression after I+VEN or G-Clb may be eligible for and choose to receive subsequent therapy with single-agent ibrutinib during the Subsequent Therapy Phase.

Subject participation will include a Screening Phase, a Treatment Phase (fixed-duration Treatment Arm A [I+VEN] or Treatment Arm B [G-Clb]), and a Follow-up Phase. Subjects from either treatment arm who subsequently develop IRC-confirmed progressive disease and have active disease requiring treatment may be eligible to receive single-agent ibrutinib until disease progression or unacceptable toxicity as part of the Subsequent Therapy Phase. Participation in this phase of the study is not mandatory and is based on investigator's discretion. 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.

SUBJECT POPULATION

Key eligibility criteria include the following: ≥65 years of age, or, 18 to 64 years of age and have at least 1 of the following, a CIRS score >6 or creatinine clearance (CrCl) <70 mL/min; active disease status per the iwCLL criteria with measurable nodal disease by CT; and Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) grade of 0, 1, or 2. Subjects with deletion of the short arm of chromosome 17 (del17p) or known *TP53* mutations are excluded.

DOSAGE AND ADMINISTRATION

Subjects randomly assigned to Treatment Arm A (I+VEN) will receive ibrutinib (420 mg/day orally) given as lead-in treatment for 3 cycles. Starting at Cycle 4, venetoclax dose ramp-up (from 20 mg to

400 mg over 5 weeks) will begin, and venetoclax will be administered with ibrutinib for 12 cycles. Subjects randomly assigned to Treatment Arm B (G-Clb) will receive G-Clb for 6 cycles. Obinutuzumab will be administered intravenously at a dose of 1000 mg on Days 1, 8 and 15 in Cycle 1. In Cycles 2 to 6, 1000 mg obinutuzumab will be given on Day 1. Chlorambucil will be administered orally at a dose of 0.5 mg/kg body weight, on Days 1 and 15 of Cycles 1 to 6. A cycle will be defined as 28 days. Subjects in the Subsequent Therapy Phase will receive continuous ibrutinib (420 mg/day orally) until disease progression or unacceptable toxicity.

EVALUATIONS

Efficacy evaluations will include imaging, physical examinations, evaluation of blood and bone marrow, disease-related symptoms, and assessment of patient-reported outcomes (PRO). Safety evaluations will include AE monitoring, physical examinations, laboratory tests, and review of concomitant medications.

To better understand the molecular and protein markers associated with response to and relapse following study treatment, bone marrow and peripheral blood samples will be collected. For subjects assigned to the I+VEN treatment arm, sparse samples will be collected for pharmacokinetic (PK) analysis.

STATISTICAL METHODS

The primary efficacy endpoint of PFS will be determined by an IRC. The study is designed to detect a hazard ratio (HR) of 0.5 for the I+VEN group relative to G-Clb group (corresponding to an improvement of 100% in median PFS [eg, from 27 months to 54 months]) with 80% power at a 2-sided significance level of 0.05. The Kaplan-Meier method will be used to estimate the PFS for each treatment group, and the stratified log-rank test will be used to compare the PFS. An independent Data Monitoring Committee (DMC) will review safety data periodically.

Time and Events Schedules

NOTE: For Screening Visits, either Table 1 or Table 2 can be used with Table 3.

Table 1: Time and Events Schedule for Treatment Arm A (Ibrutinib + Venetoclax)

TREATMENT ARM A: IBRUTINIB + VENETOCLAX (CYCLE VISIT SCHEDULE ONLY)											
Phase	**Screening**	**Treatment (1 cycle=28 days)**									**Post-treatment Post-PD Follow-Up**
Study Visits		Cycle 1-3	Cycle 3	Cycle 4				Cycle 5-6	Cycle 7-15	EOT Visit	(every 24 weeks)
Visit Day (D)	Up to 30 days prior to randomization	D1	D26	D1	D8	D15	D22	D1	D1	30 days (+7) after last dose	±7 days
Drug Administration Treatment (see Section 6)											
Ibrutinib 420 mg daily		〈---------- Continuous Daily ----------〉									
Venetoclax 400 mg daily (after ramp-up)				Dose Ramp-up				Continuous Daily through Cycle 15			
Clinic visit for study medication dispensation and accountability check		Required clinic visits on Day 1 of Cycles 1 through 8, 10, and 13. During cycles which do not require clinic attendance (Cycles 9, 11, 12, 14, and 15), dosing guidelines based on chemistry and hematology cutoffs outlined in Section 6 should be followed. Testing may be done outside of the treating institution.									
TLS risk assessment and prophylaxis		Cycle 1 Day 1	X[a]	X	X	X	X	As needed per investigator's assessment of TLS risk (see Section 6.1.2.2)			
Procedures											
Informed consent	X										
Medical history	X										
Pathology and FISH cytogenetics[b]	X										
IGHV mutational status (central lab)	X										
Buccal swab		Cycle 1 only									
ECG	X[c]										
ECOG PS	X										
CIRS score	X										
Vitals	X	Pulse/heart rate and blood pressure are expected in all protocol-specified visits[d]									
Weight	X	X		X				X			
Patient reported outcomes (EORTC QLQ-C30, EQ-5D-5L, FACIT-Fatigue)		Perform PROs on Day 1 of Cycles 1, 3, and 5 only. After Cycle 5, follow DE schedule in Table 3.								X	X[e]

TREATMENT ARM A: IBRUTINIB + VENETOCLAX (CYCLE VISIT SCHEDULE ONLY)											
Phase	**Screening**	**Treatment (1 cycle=28 days)**									**Post-treatment Post-PD Follow-Up**
Study Visits		Cycle 1-3	Cycle 3	Cycle 4				Cycle 5-6	Cycle 7-15	EOT Visit	(every 24 weeks)
Visit Day (D)	Up to 30 days prior to randomization	D1	D26	D1	D8	D15	D22	D1	D1	30 days (+7) after last dose	±7 days
Laboratory Assessments											
Serum chemistry	X	X[f]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X	
Hematology	X	X[f]	X	X				X	X	X	
CrCl (Cockcroft-Gault)	X	X[f]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]		
Coagulation panel	X										
Hepatitis testing (see Section 4.2)	X[c]										
Pregnancy test for WOCBP	X[i]	More frequent pregnancy testing may be performed as required by local regulations.									
β_2 microglobulin (local)	X			X					Cycle 10 or DE3 only	X	
MRD peripheral blood analysis		Cycle 1 only									
Biomarker blood samples[h]	X	Cycles 1&2 only		X		X				X	
Predose ibrutinib PK sample (plasma)		Cycles 2&3 only						X			
Predose venetoclax PK sample (plasma)								X			
Disease Evaluations: Will be performed every 12 weeks after randomization through Week72, then every 16 weeks through Week 152, then every 24 weeks thereafter until disease progression or death. See Table 3 for exact schedule of assessments.											
Ongoing Subject Review											
Concomitant medications	X	Continuous from the signing of ICF until 30 days after the last dose of study treatment or until the start of subsequent anti-leukemic therapy, whichever is first. Adverse events with onset >30 days after the last dose should be reported if considered related to study treatment.									
Adverse events	X										
Subsequent therapy											X
Survival status (see Section 9.1.4)											X

Abbreviations: AE=adverse event; CIRS=Cumulative Illness Rating Scale; CrCl=Creatinine clearance; CR=complete response; CT=computed tomography; D=Day; DE=disease evaluation; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EORTC QLQ=European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; EOT=end-of-treatment; EQ-5D-5L=EuroQol 5 Dimension 5 Level questionnaire; FACIT=Functional Assessment of Chronic Illness Therapy; FISH=fluorescence in situ hybridization; ICF=informed consent form; *IGHV*=immunoglobulin heavy-chain variable region; LDH=lactate dehydrogenase; MRD=minimal residual disease; PD=progressive disease; PK=pharmacokinetic; PRO=patient-reported outcome; PS=performance status; TLS=tumor lysis syndrome; WOCBP=women of childbearing potential

Footnotes:

a. The 12-week CT scan is required to assess TLS risk before the start of venetoclax (See Table 3). Sponsor approval to start Cycle 4 will be dependent on completion of TLS risk assessment.
b. Pathology report, including del17p and del11q by FISH must be sent to sponsor for review of eligibility prior to randomization.
c. ECG and viral serology results obtained within 60 days of randomization are acceptable.
d. These assessments should be recorded in source documents but will not be routinely collected in the eCRF. Clinically significant abnormalities should be recorded as AEs and reported in the eCRF.
e. After disease progression, ePRO assessment will be limited to the EQ-5D-5L questionnaire only for the first 2 Post-PD Visits.
f. Laboratory values obtained prior to Cycle 1 Day 1 should be repeated if the blood sample was collected more than 72 hours prior to the anticipated start of study treatment. Test results should satisfy eligibility criteria for treatment to commence.
g. Serum chemistry and creatinine monitoring (see Section 6.1.2.2) must be assessed as part of TLS risk assessment. Abnormalities must be corrected 2-3 days before the start of venetoclax treatment and reassessed prior to each subsequent dose increase. After Cycle 6, additional tests for assessment of TLS risk (ie, uric acid, calcium, phosphate, LDH) may be done on as needed basis as determined by the treating physician.
h. In addition to these timepoints, biomarker samples should be obtained at DE visits during which the first CR response or PD is documented (see Table 3).
i. Pregnancy testing must be done or repeated within 7 days before the first dose of study treatment.

Table 2: Time and Events Schedule for Treatment Arm B (Obinutuzumab + Chlorambucil)

TREATMENT ARM B: OBINUTUZUMAB + CHLORAMBUCIL (CYCLE VISIT SCHEDULE ONLY)									
Phase	**Screening**	**Treatment (1 cycle=28 days)**							**Post-treatment Post-PD Follow-Up**
Study Visits		Cycle 1				Cycle 2-6		EOT Visit	(every 24 weeks)
Visit Day (D)	Up to 30 days prior to randomization	D1	D2	D8	D15	D1	D15[b]	30 days (+7) after last dose	±7 days
Study Drug Administration (Section 6)									
Obinutuzumab 100 mg IV		X[a]							
Obinutuzumab 900 mg IV			X[a]						
Obinutuzumab 1000 mg IV				X	X	X			
Chlorambucil 0.5 mg/kg		X			X	X	X[b]		
IRR prophylaxis		X	X	X	X	X			
Procedures									
Informed consent	X								
Medical history	X								
Pathology and FISH cytogenetics[c]	X								
IGHV mutational status (central lab)	X								
Buccal swab		X							
ECG	X[d]								
ECOG	X								
CIRS score	X								
Vitals	X	Pulse/heart rate and blood pressure are expected in all protocol-specified visits[e]							
Weight	X	X				X			
Patient reported outcomes (EORTC QLQ-C30, EQ-5D-5L, FACIT-Fatigue)		Perform PROs on Day 1 of Cycles 1, 3, 5 only. After Cycle 5, follow DE schedule in Table 3.						X	X[f]
Laboratory Assessments									
Serum chemistry	X	X[g]		X	X	X	X[b]	X	
Hematology	X	X[g]		X	X	X	X[b]	X	
Creatinine clearance	X	X[g]				X			
Coagulation panel	X								
Hepatitis testing (Sec 4.2)	X[d]								
Pregnancy test for WOCBP	X[i]	More frequent pregnancy testing may be performed as required by local regulations.							
$\beta_2$microglobulin	X					Cycle 4 only		X	

TREATMENT ARM B: OBINUTUZUMAB + CHLORAMBUCIL (CYCLE VISIT SCHEDULE ONLY)									
Phase	**Screening**	**Treatment (1 cycle=28 days)**							**Post-treatment Post-PD Follow-Up**
Study Visits		Cycle 1				Cycle 2-6		EOT Visit	(every 24 weeks)
Visit Day (D)	Up to 30 days prior to randomization	D1	D2	D8	D15	D1	D15[b]	30 days (+7) after last dose	±7 days
MRD peripheral blood analysis		X							
Biomarker blood samples[h]	X	X				Cycle 2 & 4 only	Cycle 4 only[j]	X	
Disease Evaluations: will be performed every 12 weeks after randomization through Week 72, then every 16 weeks through Week 152, then every 24 weeks thereafter until disease progression or death. See Table 3 for exact schedule of assessments.									
Ongoing Subject Review									
Concomitant medications	X	Continuous from the signing of ICF until 30 days after the last dose of study treatment or until the start of subsequent anti-leukemic therapy, if earlier. Adverse events with onset >30 days after the last dose should be reported if considered related to study treatment.							
Adverse events	X								
Subsequent therapy									X
Survival status (see Section 9.1.4)									X

Abbreviations: AE=adverse event; CIRS=Cumulative Illness Rating Scale; CR=complete response; D=Day; DE=disease evaluation; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EORTC QLQ=European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; EOT=end-of-treatment; EQ-5D-5L=EuroQol 5 Dimension 5 Level questionnaire; FACIT=Functional Assessment of Chronic Illness Therapy; FISH=fluorescence in situ hybridization; ICF=informed consent form; *IGHV*=immunoglobulin heavy-chain variable region; IRR=infusion-related reaction; IV=intravenous; MRD=minimal residual disease; PD=progressive disease; PRO=patient-reported outcome; WOCBP=women of childbearing potential

Footnotes:

a. Split first dose between Day 1 (100 mg) and Day 2 (900 mg). For subjects who tolerate the first 100 mg well and required no dose interruption or modification of the infusion rate, the full dose may be given on Day 1 (See Section 6.2.1.1) at investigator's discretion.
b. Predose laboratory tests may be done outside the treating institution on Day 15, Cycles 2-6. The investigator is required to assess these results, recommend dose interruptions or reductions as needed, and to approve home self-administration of chlorambucil on Day 15, Cycles 2-6.
c. Pathology report, including del17p and del11q by FISH must be sent to sponsor for review of eligibility prior to randomization.
d. ECG and viral serology results obtained within 60 days of randomization are acceptable.
e. These assessments should be recorded in source documents but will not be routinely collected in the eCRF. Clinically significant abnormalities should be recorded as AEs and reported in the eCRF.
f. After disease progression, ePRO assessment will be limited to the EQ-5D-5L questionnaire only for the first 2 Post-PD Visits.
g. Laboratory values obtained prior to Cycle 1 Day 1 should be repeated if the blood sample was collected more than 72 hours prior to the anticipated start of study treatment. Test results should satisfy eligibility criteria for treatment to commence.
h. In addition to these timepoints, biomarker samples should be obtained at DE visits during which the first CR response or PD is documented (see Table 3)
i. Pregnancy testing must be done or repeated within 7 days before the first dose of study treatment.
j. This sample will be collected on subjects who are coming to clinic for on-site chlorambucil administration on Cycle 4 Day 15.

Table 3: Time and Events Schedule for Treatment and Post-Treatment Disease Evaluations Prior to Disease Progression Treatment Arm A and Treatment Arm B[a]

	Screening	Week 12	Week 24	Week 36	Week 48	Week 60	Week 72	Weeks 88 through 152	Week 176 onward
Disease Evaluation	Up to 30 days prior to randomization	DE 1	DE 2	DE 3	DE 4	DE 5	DE 6	DE 7-11 (every 16 Weeks)	DE 12 onward (every 24 Weeks)
		Note: DE1 has window of -7 days; all other DE visits have a window of ±7 days.							
CT Scan	X[b]	X[c]		X		X	X	X	X
Physical examination	X	X	X	X	X	X	X	X	X
Vitals	X	Pulse/heart rate and blood pressure are expected in all protocol-specified visits[d]							
Disease-related symptoms	X	X	X	X	X	X	X	X	X
Hematology	X	X	X	X	X	X	X	X	X
Bone marrow aspirate	X[b]			X[e]			X[e]		
Bone marrow biopsy	X[b]			X[e]			X[e]		
MRD in subjects with PR or better									
Peripheral blood MRD		X	X	X	X	X	X	X	X
Bone marrow aspirate MRD	X[b]			X[e]			X[e]		
Patient-reported outcomes (EORTC QLQ-C30, EQ-5D-5L, FACIT-Fatigue)			X	X	X	X	X	X	X
Biomarker blood samples[f]	X			X				X[g]	

Abbreviations: CR=complete response; CT=computed tomography; DE=disease evaluation; EORTC QLQ=European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D-5L=EuroQol 5 Dimension 5 Level questionnaire; FACIT=Functional Assessment of Chronic Illness Therapy; MRD=minimal residual disease; PR=partial response; PD=progressive disease; TLS=tumor lysis syndrome.

Footnotes:

a. After disease progression, follow Post-Treatment post-PD Follow-up Phase schedule of assessments in each respective treatment arm (Table 1 and Table 2).
b. Standard of care CT scans meeting the Imaging Acquisition Guidelines standard done within 60 days of randomization and a bone marrow biopsy and aspirate done within 90 days of randomization may be used for screening. For subjects undergoing a bone marrow biopsy and aspirate during the screening, a sample of the aspirate and biopsy should be collected for biomarker assays and MRD testing. Archived bone marrow slides for biomarkers are acceptable.
c. The 12-week CT scan is critical to assess TLS risk at the end of Cycle 3. This scan is required for both Treatment Arm A and Treatment Arm B.
d. These assessments should be recorded in source documents but will not be routinely collected in the eCRF. Clinically significant abnormalities should be recorded as AEs and reported in the eCRF.
e. For all subjects with a response of PR or better, a bone marrow aspirate and biopsy must be obtained and central assessment of bone marrow aspirate for MRD must be performed at DE3. The bone marrow aspirate and biopsy should be sent to a local laboratory for standard evaluation and response assessment. At DE6, a central bone marrow aspirate MRD assessment is required in all subjects with a response of PR or better. Bone marrow biopsy and aspirate for local evaluations are only required for subjects on the I+VEN treatment arm who were not confirmed CR at DE3. For subjects with a suspected PD based on new onset cytopenia, a bone marrow aspirate and biopsy should be obtained to confirm PD. A sample of the bone marrow aspirate, as well as bone marrow biopsy slides, should be sent to the sponsor for additional biomarker analyses.
f. At DE3 and at any DE visit during which the first CR response or PD is documented.
g. A blood sample for biomarker assessments will be collected at DE8.

Table 4: Time and Events Schedule for Subsequent Therapy with Single-agent Ibrutinib

Phase		**Subsequent Therapy (1 cycle = 28 days)**				**End-of-Treatment**	**Post-treatment, Post-PD Follow-up**
Study Visit		Cycle Visits[a]			DE Visits	EOT Visit	
	Up to 30 days prior to Cycle 1	Cycle 1 Day1	Cycle 5 Day 1	All other cycle visits as indicated in Figure 2	Every 16 weeks × 3, then every 24 weeks until progression (±7 days)	30 days (+7) after last dose	Every 24 weeks (±7 days)
Study Drug Administration (see Section 6)							
Ibrutinib 420 mg daily		<---------- Continuous Daily ---------->					
Procedures							
Review of informed consent[b]	X						
Disease-related symptoms	X				X		
Physical examination	X				X		
Medical History[c]	X						
CIRS score[c]	X						
ECOG PS	X						
ECG	X						
Vitals	X	Pulse/heart rate and blood pressure are expected in all protocol-specified visits[d]					
Weight	X						
FISH cytogenetics	X						
Laboratory Assessments							
Serum chemistry	X	X	X	X[e]		X	
Hematology	X	X	X	X[e]	X	X	
Hepatitis testing (Section 4.2)	X						
Pregnancy test for WOCBP	X[f]	More frequent pregnancy testing may be performed as required by local regulations.					
Efficacy Assessments							
CT scan[g]	X				X		
Biomarker blood samples		X	X		X (if PD or CR)	X	
Ongoing Subject Review							
Concomitant medication	Continuous from 30 days prior to start of single-agent ibrutinib to 30 days after the last dose of subsequent therapy, or until the start of subsequent anti-leukemic therapy, if earlier. AEs with onset >30 days after the last dose should be reported if considered related to ibrutinib.						
Adverse events							
Survival status							X
Subsequent therapy (following single-agent ibrutinib)							X

Abbreviations: AE=adverse event; CR=complete response; CT=computed tomography; DE=disease evaluation; EOT=end-of-treatment; FISH=fluorescence in situ hybridization; G-Clb=obinutuzumab plus chlorambucil; I+VEN= ibrutinib plus venetoclax; PD=progressive disease; WOCBP=women of childbearing potential.

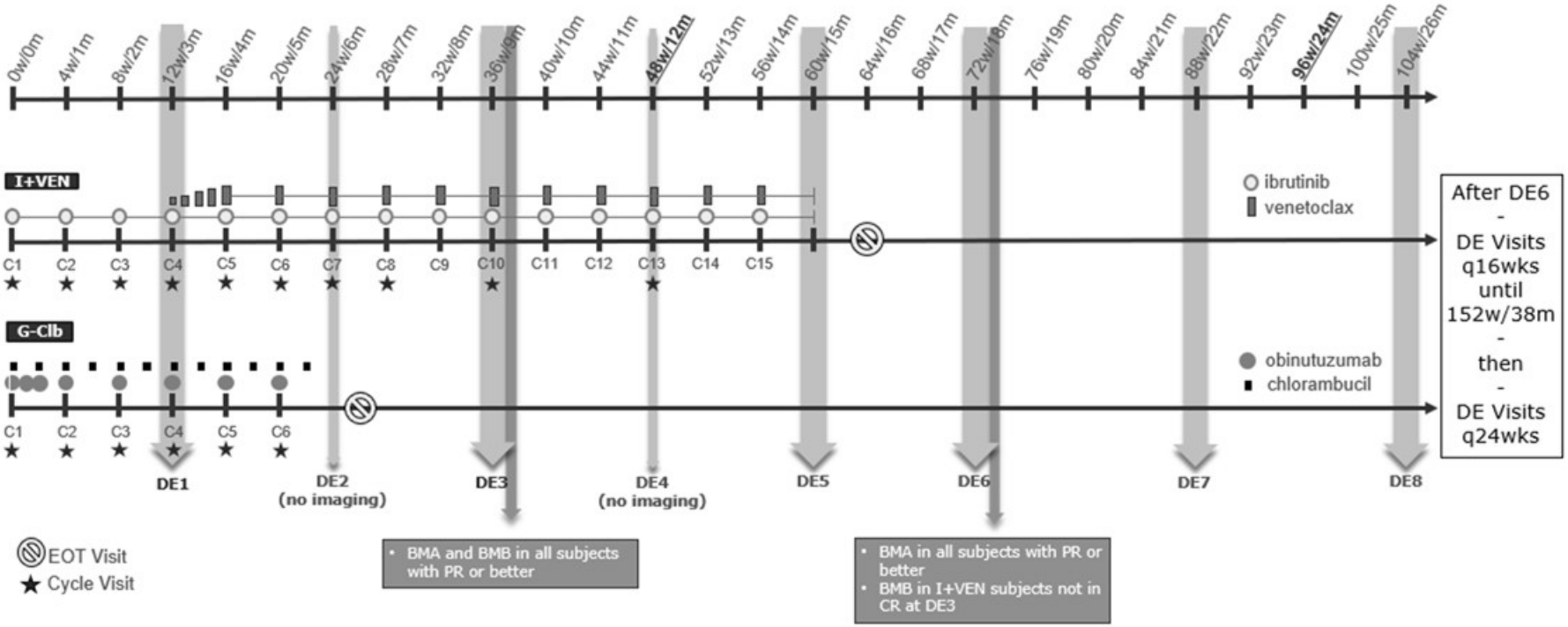
Footnotes:

a. Cycle visits at the study site are required on Cycles 1, 2, and 3, then every 2 cycles until Cycle 13 and every 3 cycles thereafter.

b. The investigator is expected to re-review the informed consent with the subject to ensure that he or she understands the purpose of, as well as the study procedures and required visits associated with, the Subsequent Therapy Phase.

c. Only new medical conditions that have developed since the initial screening period or medical conditions that have worsened since baseline should be reported in the eCRF. CIRS score should be re-evaluated if new or worsening medical conditions are reported.
d. These assessments should be recorded in source documents but will not be routinely collected in the eCRF. Clinically significant abnormalities should be recorded as AEs and reported in the eCRF.
e. Testing may be done outside of the treating institution for non-cycle visits.
f. Pregnancy testing must be done or repeated within 7 days before the first dose of study treatment.
g. In the Subsequent Therapy Phase, CT imaging is expected for subjects who were initially treated with I+VEN (Treatment Arm A); this will occur at the following timepoints: baseline, Week 16, Week 48, and annually thereafter coinciding with the DE visits until progression. CT imaging studies meeting the Imaging Acquisition Guidelines done within 60 days of start of single-agent ibrutinib can be used as baseline. For subjects who were initially treated with G-Clb (Treatment Arm B), imaging is recommended only when clinically indicated and as determined by the investigator.

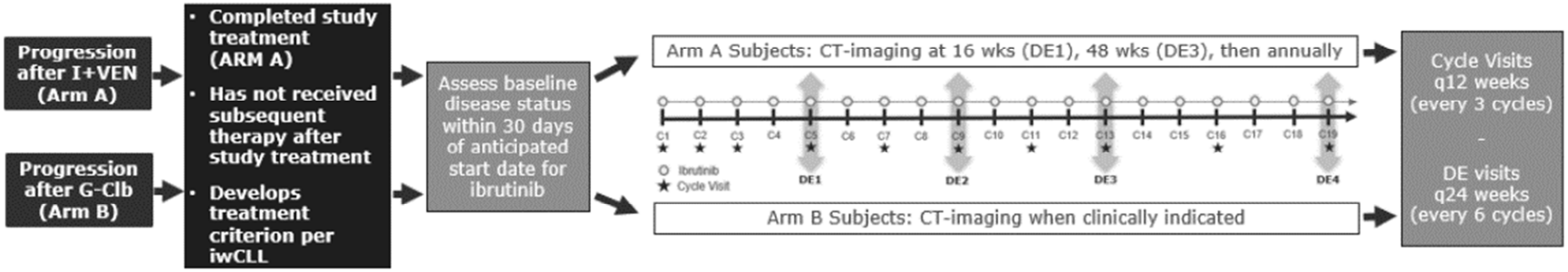
Figure 1: Disease Evaluation and Treatment Schedule



Abbreviations: BMA=bone marrow aspirate; BMB=bone marrow biopsy; C=Cycle; CR=complete response; DE=disease evaluation; EOT=end-of-treatment; G-Clb=obinutuzumab and chlorambucil; I+VEN=ibrutinib plus venetoclax; m=month; PR=partial response; w=week.

Notes:
0w/0m corresponds to date of randomization.
DE visits will occur every 12 weeks until DE6 at 72 weeks, then every 16 weeks until 152 weeks, then every 24 weeks until progression or death.
Imaging at 12, 36, 60, and 72 weeks, then every 16 weeks x 5, then every 24 weeks until progression or death. At DE visits that do not include a CT scan (24 and 48 weeks), the preceding radiographic assessment should be considered together with the current physical examination and peripheral blood evaluation in assessing the overall response for the visit.

Figure 2: Disease Evaluation and Treatment Schedule for Subsequent Therapy with Single-agent Ibrutinib



Abbreviations: C=Cycle; CT=computed tomography; DE=disease evaluation; G-Clb=obinutuzumab plus chlorambucil; I+VEN=ibrutinib plus venetoclax; iwCLL=International Workshop on Chronic Lymphocytic Leukemia.

ABBREVIATIONS

AE	adverse event
ALC	absolute lymphocyte count
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
β-hCG	β-human chorionic gonadotropin
BCL-2	B-cell lymphoma-2
BCR	B-cell receptor
BTK	Bruton's tyrosine kinase
CBC	complete blood count
CI	confidence interval
CIRS	Cumulative Illness Rating Scale
CIT	chemoimmunotherapy
CLL	chronic lymphocytic leukemia
CNS	central nervous system
CR	complete response
CrCl	creatinine clearance
CRi	complete response with an incomplete marrow recovery
CT	computed tomography
CYP	cytochrome p450
del11q	deletion of the long arm of chromosome 11
del17p	deletion of the short arm of chromosome 17
DMC	Data Monitoring Committee
DE	disease evaluation
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
eDC	electronic data capture
EORTC QLQ	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire
EQ-5D-5L	EuroQol 5 Dimension 5 Level questionnaire
ESMO	European Society for Medical Oncology
EU	European Union
FACIT	Functional Assessment of Chronic Illness Therapy
FCR	fludarabine, cyclophosphamide, and rituximab
FISH	fluorescence in situ hybridization
G-Clb	obinutuzumab plus chlorambucil
GCP	Good Clinical Practice
HIV	human immunodeficiency virus
HR	hazard ratio
I+VEN	ibrutinib plus venetoclax
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
IGHV	immunoglobulin heavy-chain variable region
ILD	interstitial lung disease
INR	international normalized ratio
IRB	Institutional Review Board
IRC	Independent Review Committee
IRR	infusion-related reaction
ITT	intent-to-treat
iwCLL	International Workshop on Chronic Lymphocytic Leukemia
IWRS	Interactive Web Response System
MRD	minimal residual disease

MRI	magnetic resonance imaging
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NGS	next-generation sequencing
nPR	nodular partial response
ORR	overall response rate
OS	overall survival
PCR	polymerase chain reaction
PD	progressive disease
PFS	progression-free survival
P-gp	P-glycoprotein
PQC	Product Quality Complaint
PR	partial response
PRL	partial response with lymphocytosis
PRO	patient-reported outcome(s) (paper or electronic as appropriate for this study)
PS	Performance Status
SAE	serious adverse event
SAP	Statistical Analysis Plan
SIPPM	Site Investigational Product Procedures Manual
SLL	small lymphocytic lymphoma
TEAE	treatment-emergent adverse event
TLS	tumor lysis syndrome
ULN	upper limit of normal
US	United States
VAF	variable allele frequency
VAS	visual analog scale

1. INTRODUCTION

1.1. Chronic Lymphocytic Leukemia

CLL and SLL are characterized by a spectrum of clinical manifestations, ranging from indolent disease requiring no treatment for decades, to markedly aggressive disease that requires urgent intervention.[8,25] The International Workshop on Chronic Lymphocytic Leukemia (iwCLL) developed guidelines to define the clinical context by which treatment should be initiated. These include progressive marrow failure (manifested by anemia or thrombocytopenia or both); massive or progressive splenomegaly; massive lymphadenopathy; progressive lymphocytosis with a rapid lymphocyte doubling time; worsening autoimmune cytopenias; or significant constitutional symptoms.[28] Throughout this protocol, use of the term “CLL” refers to CLL and SLL.

The term "sponsor" used throughout this document refers to the entities listed in the Contact Information page(s), which will be provided as a separate document.

1.2. Treatment of Chronic Lymphocytic Leukemia

The type and intensity of initial therapy is guided by multiple factors. Patient age; presence or absence of comorbidities; and clinical or molecular disease risk features are foremost among them. Current treatment guidelines from the European Society for Medical Oncology (ESMO) indicate that the choice of treatment for patients with previously untreated CLL should be based on the stage of disease, whether a patient is considered fit, and the presence or absence of deletion of the short arm of chromosome 17 (del17p) or *TP53* mutation.[15,18] Given the median age at diagnosis and first treatment of CLL, many patients fall into the “less fit” category.

For patients who are less fit due to comorbidities and have CLL without del17p or *TP53* mutation, single-agent ibrutinib, or chlorambucil in combination with an anti-CD20 antibody (rituximab, ofatumumab, or obinutuzumab) are the recommended frontline treatment options.[16] Data from randomized controlled clinical studies have shown that the addition of a newer anti-CD20 antibody, such as obinutuzumab, or ofatumumab, to chlorambucil provides improvement in median progression-free survival (PFS) compared with chlorambucil alone or rituximab plus chlorambucil.[24,33] Median PFS after treatment with obinutuzumab plus chlorambucil (G-Clb) was 26.7 months, while median survival was not reached.[23] Overall response was 77% with a 22% complete response (CR)/complete response with an incomplete marrow recovery (CRi) rate. MRD-negative remissions, defined as detection of <1 CLL cell in 10,000 normal leukocytes by either polymerase chain reaction (PCR) assay or flow cytometry, were reported for 41% and 19% of the subjects with CR/CRi in peripheral blood and bone marrow, respectively.[21] Anti-CD20 therapy administered in combination with cytotoxic chemotherapy to patients with CLL is often associated with increased rates of severe neutropenia (26% to 35%), or Grade 3 or higher infusion reactions (7% to 9% for rituximab, 10% for ofatumumab, 21% for obinutuzumab).[22,33,46]

Ibrutinib is approved for the treatment of CLL (including del17p CLL). In the Phase 3 RESONATE-2 study (PCYC-1115-CA) of first-line treatment of older patients with CLL, single-agent ibrutinib resulted in superior PFS (HR=0.16; P<0.001), OS (HR=0.16, p=0.0010) and ORR (86% vs. 35%, p<0.001) compared with chlorambucil.[3] Adverse events (AEs) of any grade that occurred in at least 20% of the patients receiving ibrutinib included diarrhea, fatigue, cough, and nausea, and were mainly Grade 1-2. At median follow-up of 18.4 months, 87% of the patients in the ibrutinib group continued on therapy.[3] Responses with single-agent ibrutinib are most often partial, although with longer follow-up, the quality of response improves and a higher rate of CR is achieved.[4] Resolution of adenopathy is usually rapid, with efflux of cells into the blood, resulting in a transient lymphocytosis. These lymphocytes are composed of quiescent cells with inhibited signaling, activation and proliferation. This early lymphocytosis does not represent treatment failure.[30] Ibrutinib treatment also is associated with rapid clearance of the disease from the spleen, and to a lesser extent, from the bone marrow, resulting in an overall reduction in tumor burden.[19,31,56]

For patients with active disease and who are considered "fit", the combination of fludarabine, cyclophosphamide and rituximab (FCR) is the standard first-line therapy. In a randomized study, CR was reported in 44% of patients treated with FCR and median PFS was approximately 5 years.[20,29] MRD-negative remissions have been reported after FCR treatment, with rates of approximately 40%-60% in peripheral blood and 30% in bone marrow in the total population. Undetectable-MRD has been shown to correlate with longer PFS and OS in FCR-treated patients.[2,51] MRD-negative remissions occur less frequently in patients with CLL with unmutated immunoglobulin heavy-chain variable region (*IGHV*) or del17p/*TP53* mutations. Toxicity limits the use of FCR in older patients or those with comorbid conditions.[52] For older but fit patients, bendamustine plus rituximab is also an option, although efficacy is lower than with FCR.[14,15]

For patients with del17p or *TP53* mutations, the recommended therapy is ibrutinib. Idelalisib plus rituximab or venetoclax are also options if the patient is not suitable for ibrutinib or alternative therapies. Chemoimmunotherapy (CIT) regimens tend to show limited efficacy in patients with del17p/*TP53* mutation, whereas the newer B-cell receptor (BCR)-targeted therapies have demonstrated efficacy across poor prognostic groups.[37,57]

1.3. Ibrutinib

Ibrutinib (IMBRUVICA®) is an orally administered, covalently-binding inhibitor of Bruton's tyrosine kinase (BTK) co-developed by Pharmacyclics LLC, an AbbVie Company, and Janssen Research & Development LLC for the treatment of B-cell malignancies. It has been approved for use in many regions, including the United States (US) and European Union (EU). There are currently a number of indications approved, including for the treatment of patients with CLL, including CLL with del17p, patients with mantle cell lymphoma who have received at least 1 prior therapy, patients with Waldenström's macroglobulinemia, patients with marginal zone lymphoma who require systemic therapy and have received at least one prior anti-CD20-based therapy, and adult patients with chronic graft versus host disease following the failure of 1 or more lines of systemic therapy.

For the most comprehensive nonclinical and clinical information regarding ibrutinib, refer to the latest version of the ibrutinib Investigator's Brochure (IB) and Addenda.

1.3.1. Clinical Studies

1.3.1.1. Clinical Pharmacokinetics

For a comprehensive summary of clinical pharmacokinetics, please refer to the latest version of the ibrutinib IB and Addenda.

1.3.1.2. Clinical Efficacy

1.3.1.2.1. Ibrutinib Monotherapy and in Combination with Chemoimmunotherapy in CLL

Data from 3 randomized, Phase 3 studies demonstrated the efficacy of ibrutinib monotherapy in subjects with treatment-naïve and previously treated CLL (compared with chlorambucil in Study PCYC-1115-CA and ofatumumab in Study PCYC-1112-CA), and when used in combination with CIT in subjects with previously treated CLL (in combination with bendamustine and rituximab in Study CLL3001) (Table 5). For a list of ongoing studies, please refer to the ibrutinib IB.

Table 5: Efficacy Summary From Phase 3 Studies of Ibrutinib in CLL

Study Number/Design	Study Population	Ibrutinib Dosing Schedule	Efficacy Results
PCYC-1115-CA: Phase 3, randomized, open-label, comparator (ibrutinib vs. chlorambucil), monotherapy study in subjects ≥65 years of age	Treatment-naïve CLL	420 mg/day	Ibrutinib superior to chlorambucil Median time on study: 18.4 months ibrutinib arm 18.4 months chlorambucil arm PFS[a,b]: HR 0.161 (95% CI: 0.091, 0.283), p<0.0001 Median PFS[a,b]: NR ibrutinib vs. 18.9 months chlorambucil ORR[b,c]: 82.4% ibrutinib vs. 35.3% chlorambucil, p<0.0001 ORR including PRL[b,c]: 86.0% ibrutinib vs. 35.3% chlorambucil, p<0.0001 OS[c]: HR 0.163 (95% CI: 0.048, 0.558), p=0.0010
PCYC-1112-CA: Phase 3, randomized, open-label, comparator (ibrutinib vs. ofatumumab), monotherapy study	Relapsed or refractory CLL	420 mg/day	Ibrutinib superior to ofatumumab Median time on study: 9.6 months ibrutinib arm 9.2 months ofatumumab arm PFS[a,b]: HR 0.215 (95% CI: 0.146, 0.317), p<0.0001 Median PFS[a,b]: NR ibrutinib vs. 8.1 months ofatumumab ORR[b,c]: 42.6% ibrutinib vs. 4.1% ofatumumab, p<0.0001 ORR including PRL[b,c]: 62.6% ibrutinib vs. 4.1% ofatumumab, p<0.0001 OS[c]: HR 0.434 (95% CI: 0.238, 0.789), p=0.0049
PCI-32765CLL3001: Phase 3, randomized, double-blinded, placebo controlled (ibrutinib+BR vs. placebo+BR), combination therapy study	Relapsed or refractory CLL	420mg/day	Ibrutinib+BR superior to placebo +BR Median time on study: 17.2 months ibrutinib+BR arm 16.8 months placebo+BR arm PFS[a,b]: HR=0.203 (95% CI: 0.150, 0.276), p<0.0001 Median PFS[b]: NR ibrutinib+BR vs. 13.3 months placebo+BR ORR[b,c]: 82.7% ibrutinib+BR vs. 67.8% placebo+BR, p<0.0001 MRD-negative response rate[c]: 12.8% ibrutinib+BR vs. 4.8% placebo+BR OS[c]: HR=0.628 (95% CI: 0.385, 1.024), p=0.0598

BR=bendamustine and rituximab; CI=confidence interval; CLL=chronic lymphocytic leukemia; HR=hazard ratio; MRD=minimal residual disease; NR=not reached; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; PRL=partial response with lymphocytosis; SLL=small lymphocytic lymphoma.

Footnotes:

a. Primary endpoint
b. IRC assessed
c. Secondary endpoint

1.3.1.3. Clinical Safety

For the most comprehensive clinical safety information, please refer to the latest version of the ibrutinib IB and Addenda, including Section 5 Summary of data and guidance for the investigator.

Monotherapy Studies

As of 31 July 2017, 1523 subjects have been treated with ibrutinib monotherapy in sponsor-initiated clinical studies in B-cell lymphomas. The most frequently reported treatment-emergent adverse events (TEAEs) in subjects receiving ibrutinib as monotherapy (N=1523) are listed in Table 6.

Table 6: Most Frequently Reported TEAEs in Subjects Receiving Ibrutinib as Monotherapy

Most Frequently Reported TEAEs ≥15%[a]	Most Frequently Reported Grade 3 or 4 TEAEs ≥3%[a]	Most Frequently Reported Serious TEAEs ≥2%[b]
Diarrhea	Neutropenia	Pneumonia
Fatigue	Pneumonia	Atrial fibrillation
Nausea	Thrombocytopenia	Pyrexia
Cough	Anemia	Febrile neutropenia
Pyrexia	Hypertension	
Anemia	Diarrhea	
Upper respiratory tract infection	Atrial fibrillation	
Neutropenia	Fatigue	
Edema peripheral		
Thrombocytopenia		
Muscle spasms		

Abbreviation: TEAE=treatment-emergent adverse event
[a] Source: Table 5 of ibrutinib IB (Version 11)
[b] Source: Table 6 of ibrutinib IB (Version 11)

Combination Studies

Refer to the integrated data from combination therapy studies in subjects with B-cell malignancies in the latest version of the ibrutinib IB for a summary of the most frequently reported AEs observed with ibrutinib in combination studies. The overall safety profile of ibrutinib in combination with various chemo- and immunotherapies was consistent with the known safety profiles of ibrutinib and the background regimens evaluated, with no new safety signals identified for ibrutinib.

Risks

An overview of the potential risks associated with the administration of ibrutinib based on sponsor-initiated clinical studies is presented in the ibrutinib IB. A summary of risks is presented in Attachment 1. Unanticipated side effects that have not been previously observed may occur.

1.4. Venetoclax

Venetoclax is an oral inhibitor of B-cell lymphoma-2 (BCL-2), an anti-apoptotic protein. Overexpression of BCL-2 has been demonstrated in CLL cells where it mediates tumor cell survival and has been associated with resistance to chemotherapy. The approved indications include the use of venetoclax monotherapy for the treatment of CLL in the presence of del17p or *TP53* mutation in adult patients who are unsuitable for or have failed a BCR pathway inhibitor, and for the treatment of CLL in the absence of del17p or *TP53* mutation in adult patients who have failed both CIT and a BCR pathway inhibitor. It is currently in development in combination with immunotherapy (rituximab or obinutuzumab) for the treatment of the broad population of relapsed/refractory CLL, as well as frontline CLL.

In a Phase 1 study in patients with relapsed or refractory CLL (n=116), venetoclax treatment resulted in a 79% ORR, with a 20% rate of CR/CRi. Of the subjects with CR/CRi, 35% of those with available samples were shown to be MRD-negative in the bone marrow (5% of total population). Adverse events included mild diarrhea (in 52% of the patients), upper respiratory tract infection (48%), nausea (47%), and Grade 3 or 4 neutropenia (41%).[47] Tumor lysis syndrome (TLS) is an important identified risk when initiating venetoclax. In the initial Phase 1 dose-finding studies, which had a short titration phase and higher starting dose, the incidence of TLS was 13% and included 2 fatal events and 3 events of acute renal failure. However, the risk of TLS was reduced to 3% after revision of the dosing regimen and modification to prophylaxis and monitoring measures.[54] In a Phase 2 study in relapsed patients with the poor prognostic cytogenetic abnormality, del17p (n=107), a 79% ORR and 8% CR/CRi rate were observed.[50] The MRD-negative CR rate was 3%.[53]

1.5. Ibrutinib in Combination with Venetoclax in CLL

Ibrutinib and venetoclax have complementary mechanisms of action targeting distinct B-cell pathways involved in the propagation of CLL cells. Ibrutinib arrests CLL cell proliferation. Venetoclax is pro-apoptotic and induces early cell death.[11,42] Ibrutinib also affects the adhesion and migration of CLL cells resulting in rapid efflux of CLL cells from tissue compartments, especially lymph node and spleen, into the peripheral blood. Venetoclax treatment results in effective clearance of the blood and bone marrow, but residual disease can be observed in lymph nodes. Together the 2 drugs are expected to provide complementary and effective clearance of disease from all compartments.

Preclinical studies evaluating CLL patient samples have demonstrated a surge in cellular apoptosis with concomitant inhibition of BTK and BCL-2 suggesting that the combination of ibrutinib plus venetoclax (I+VEN) is synergistic.[6,42] A high-throughput screen combining ibrutinib with a number of novel agents revealed venetoclax to be the most synergistic combination partner across several B-cell malignancies.[48] In a study to evaluate samples from patients treated with ibrutinib monotherapy to explore drugs that may have a synergistic effect with ibrutinib in facilitating cell death, venetoclax had the most potent cell killing. Ibrutinib decreased levels of myeloid cell leukemia 1, an anti-apoptotic protein, which is thought to explain, in part, the greater apoptosis seen with venetoclax when given in combination.[6] Furthermore, ibrutinib treatment may generate overexpression of BCL-2 which increases cell sensitivity to venetoclax.[10,17] This induction of CLL cell dependence on BCL-2 further supports synergy in concomitant use of venetoclax with ibrutinib. In a T-cell leukemia-1 adoptive transfer mouse model of CLL, the combination of I+VEN resulted in a more complete and durable response compared with either of the single agents alone.[49] Early clinical data from an ongoing, investigator-initiated study of the combination of I+VEN in patients with high-risk relapsed/refractory CLL (CLARITY Study) indicate that the combination is highly effective, with rapid clearance of disease and acceptable tolerability.[32,34] In this study, patients are treated with ibrutinib for 8 weeks before venetoclax is started with the recommended 5-week ramp-up to 400 mg/day. Treatment will continue for a period of 14 to 26 months, depending on MRD-negative status. Among the first 35 patients who have received 4 months of therapy (including 8 weeks of the combination I+VEN) a rapid reduction in CLL cells in the peripheral

blood was observed, (median 3-log reduction). All 25 patients who have reached their 8-month response assessments (including 6 months of I+VEN) have had an objective response: 15/25 (60%) achieved CR or CRi and 7/25 (28%) have achieved an MRD-negative remission in bone marrow. Tolerability was generally reported as good, with most AEs being Grade 1 or 2. There was a single case of Grade 3 asymptomatic TLS.[32] More recent data as of December 2018 show that after 12 months of combined therapy (I+VEN), all patients have responded and 23/40 (58%) have achieved a complete remission. In addition, 27/31 (87%) had no morphological evidence of CLL in the bone marrow biopsy and 32/34 (94%) had less than 1% CLL cells in the bone marrow aspirate. Undetectable-MRD (ie <0.01%) was achieved in 23/40 (58%) patients in the peripheral blood and in 17/41 (41%) in the bone marrow.[35]

Another investigator-initiated study is evaluating the combination of I+VEN in subjects with relapsed/refractory CLL and in treatment-naïve subjects with CLL with at least 1 of the following high-risk features: del17p, mutated *TP53*, deletion of the long arm of chromosome 11, unmutated *IGHV*, or ≥65 years of age.[38] Subjects were treated with single-agent ibrutinib for 3 months, followed by addition of venetoclax with a weekly dose escalation to the target dose of 400 mg daily. The primary endpoint is rate of CR/CRi. With a median follow-up of 7.5 months (range, 0.6-12.1 months), 61 subjects have completed treatment with single-agent ibrutinib and begun the combination with I+VEN. Three months of single-agent ibrutinib therapy reduced the TLS risk category for venetoclax treatment in 51% of subjects (ie, TLS risk decreased from high- or medium-risk categories to medium- or low-risk). In the 14 subjects with relapsed/refractory CLL who have completed at least 3 months of combination therapy, 100% had a response (9 CR/CRi, 5 partial response [PR]). In the 16 subjects with treatment-naïve, high-risk CLL who completed at least 3 months of the combination, 100% had a response (9 CR/CRi, 7 PR). Across both cohorts, 6 subjects were MRD-negative by Month 9. No unexpected AEs were observed. Grade 3-4 neutropenia and Grade 3-4 thrombocytopenia were reported in 44% and 4% of subjects, respectively. There was 1 case of asymptomatic TLS, and no cases of clinical TLS.[38] Recently reported results involving the treatment-naïve cohort show that at 6 months of the combination treatment, 24/34 (71%) patients achieved CR/CRi and 14/34 (41%) achieved bone marrow undetectable-MRD remission. After 12 months of the combination, 23/25 (92%) of the patients were in CR/CRi with 17/25 (68%) achieving bone marrow undetectable-MRD remission.[39]

Study PCYC-1142-CA is an ongoing multicenter, Phase 2 study in subjects with treatment-naïve CLL. Treatment consists of open-label I+VEN for approximately 15 months. Subjects who attain MRD-negative status at Month 15 are randomized in a double-blind fashion to receive continuous treatment with ibrutinib or placebo until MRD-positivity, disease progression, or unacceptable toxicity. In the initial safety run-in of the study, a 3-month lead-in of single-agent ibrutinib before adding the venetoclax per standard dose ramp-up schedule, was tested in 14 patients. No TLS was observed during the initial safety run-in. Early data presented after 163 patients were enrolled showed an ORR of 100% in the 14 safety run-in patients (1/14 confirmed CR and 13/14 PR). Nine of 11 assessed patients had MRD-negative status in peripheral blood. Adverse events occurring in ≥20% of I+VEN exposed subjects included diarrhea (39%), fatigue (23%), nausea (23%), and arthralgia (21%). Grade 3 or higher AEs that

occurred in ≥3% of subjects included neutropenia (10%), hypertension (3%), and thrombocytopenia (3%). No clinical TLS was observed in this phase of the study.[56]

Based on preliminary data from the same study, venetoclax exposure (AUC) at 400 mg once daily appears to be approximately 1.7-fold higher with 420 mg ibrutinib (CLL, N=32) compared to venetoclax single-agent 400 mg daily exposure. Within the same dataset, ibrutinib exposures when dosed in combination with venetoclax were comparable to that observed at 420 mg of ibrutinib as a single agent. To date, no new safety signals have been identified, and investigators are advised to monitor subjects closely for signs of toxicity.

1.6. Overall Rationale for the Study

This study is designed to evaluate whether the combination I+VEN will result in superior efficacy following a fixed duration of drug administration, compared with the combination G-Clb, in the first-line treatment of subjects with CLL. Obinutuzumab in combination with chlorambucil, given for the standard duration of 6 months, is indicated for the treatment of adult patients with previously untreated CLL and comorbidities that make them unsuitable for fludarabine-based therapy. Obinutuzumab in combination with chlorambucil was chosen as the comparator for this study based on its efficacy and safety. It is a standard of care given with fixed duration and is recommended by both US and EU treatment guidelines for use in this patient population.[15,16,18,40]

As single agents, both ibrutinib and venetoclax have demonstrated efficacy and acceptable safety for the treatment of patients with CLL. The combination of I+VEN was chosen based on complementary mechanisms of action of the drugs, preclinical synergistic activity, and promising early clinical data as described in Section 1.5. In the frontline treatment of CLL, ibrutinib monotherapy has demonstrated significant PFS and OS advantages compared with chlorambucil. However, CR occurs in approximately 20% of patients and undetectable-MRD has been reported rarely.[1,3] Continuous therapy has been considered necessary to maintain the benefit of ibrutinib therapy, and continuous therapy is associated with increasing depth of response over time. Although ibrutinib has demonstrated efficacy and tolerability advantages in frontline treatment, some patients and physicians prefer fixed-duration alternatives, such as chlorambucil plus obinutuzumab, as their initial therapy to avoid long-term treatment. The strategy of combining ibrutinib with venetoclax is anticipated to result in higher rates of disease clearance in all body compartments as reflected by robust MRD-negativity and durable responses thus allowing discontinuation of therapy following a defined period of treatment. Development of the I+VEN regimen could provide patients with an effective alternative dosing option to continuous ibrutinib therapy and the clarity of knowing the length of their treatment period. Treating for a fixed duration, rather than until progression, may also preserve sensitivity to ibrutinib and venetoclax and allow for retreatment with either agent at the time of relapse. To investigate this, subjects who relapse or progress after first-line treatment with fixed-duration I+VEN (Treatment Arm A) may receive continuous single-agent ibrutinib, if eligible, in the Subsequent Therapy Phase.

During the Treatment Phase, subjects in this study will receive ibrutinib for 15 cycles (1 cycle=28 days). Venetoclax dose ramp up will begin at Cycle 4 and treatment with venetoclax will continue for 12 cycles (see Section 6.1). The rationale for the lead-in treatment with ibrutinib is to minimize the risk of TLS reported with venetoclax. TLS is a well-described phenomenon associated with treatment with venetoclax. Recent analysis of data from 3 studies of single-agent ibrutinib in relapsed/refractory and treatment-naïve CLL (N=424) demonstrated that the majority of patients who were at high risk for TLS at baseline on the basis of lymph node bulk and absolute lymphocyte count (ALC) were reduced to medium- or low-risk TLS categories within approximately 2 to 4 months of ibrutinib treatment.[55] The approach of treating with single-agent ibrutinib prior to commencing treatment with venetoclax has been utilized in the ongoing Phase 2 studies of I+VEN described previously and appears to be successful in reducing TLS risk.

In the Subsequent Therapy Phase, eligible subjects initially treated with either I+VEN or G-Clb will receive single-agent ibrutinib until disease progression or unacceptable toxicity. Subjects who initially responded to fixed-duration treatment with I+VEN are expected to retain sensitivity to ibrutinib, supporting the use of the same agent after disease relapse. For subjects previously treated with G-Clb, single-agent ibrutinib is an appropriate and approved second-line treatment option.

The population of subjects selected for this study are those considered suitable for treatment with the comparator, obinutuzumab in combination with chlorambucil, ie, adult patients with previously untreated CLL and comorbidities that make them unsuitable for fludarabine-based therapy. Subjects with del17p or known *TP53* mutation are excluded because chlorambucil plus CD20 antibody is not recommended therapy for such patients per ESMO guidelines. Subjects will be stratified based on *IGHV* mutational status and presence of del11q, as these are known prognostic factors for efficacy outcomes in the treatment of CLL.

2. OBJECTIVES, ENDPOINTS, AND HYPOTHESIS

2.1. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To compare the PFS of I+VEN with that of G-Clb	• PFS, as assessed by an IRC, the duration from date of randomization to date of disease progression or death, whichever occurs first
Secondary	
• To compare the MRD-negative remission rate of I+VEN with that of G-Clb	• Proportion of subjects who reach MRD-negative disease status (ie, <1 CLL cell per 10,000 leukocytes or <0.01%) in the bone marrow
• To compare the ORR and CR rate of I+VEN with that of G-Clb • To determine the response duration	• Rate of CR and rate of ORR (CR, CRi, nodular PR [nPR], and PR) for at least 2 months, based on IRC • Duration in days from the date of initial documentation of a response to the date of first documented evidence of progressive disease (PD) or death
• To compare OS of I+VEN with that of G-Clb	• Measured from the date of randomization to the date of death from any cause
• To compare time-to-next treatment of I+VEN with that of G-Clb	• The time from date of randomization to the start date of any anti-leukemic therapy subsequent to the study treatment
• To compare patient-reported health status and fatigue of I+VEN with that of G-Clb	• Time to worsening in functional status and fatigue, as measured by the EuroQol 5 Dimension 5 Level questionnaire (EQ-5D-5L), the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ)-C30, and the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue scale
• To evaluate the safety profile of I+VEN in subjects with previously untreated CLL	• Safety parameters including AEs and laboratory tests
• To compare hematologic improvement of I+VEN with that of G-Clb	• Improvement in hemoglobin lasting for 56 days without transfusions or growth factors • Improvement in platelets lasting for 56 days without transfusions or growth factors
• To evaluate the trough levels of ibrutinib and venetoclax when given in combination	• Descriptive statistics of ibrutinib and venetoclax trough levels in plasma
Exploratory	
• To examine molecular and protein markers associated with response to and relapse following study treatment • To examine response to subsequent therapy with single-agent ibrutinib	• Next-generation sequencing (NGS) and gene expression profiling analyses • ORR in subjects who received single-agent ibrutinib

2.2. Hypothesis

Treatment with the combination of I+VEN will result in longer PFS compared with G-Clb in subjects with previously untreated CLL.

3. STUDY DESIGN AND RATIONALE

3.1. Overview of Study Design

This is a randomized, open-label, multicenter, Phase 3 study to determine the efficacy and safety of the combination of I+VEN, compared with G-Clb, administered to subjects with previously untreated CLL who meet the iwCLL treatment criteria.

Approximately 200 subjects will be randomly assigned in a 1:1 ratio to either Treatment Arm A (I+VEN) or Treatment Arm B (G-Clb). Stratification factors will include the *IGHV* 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 Treatment Arm A (I+VEN) will receive ibrutinib for 15 cycles (1 cycle=28 days), starting with 3 cycles of ibrutinib monotherapy. Venetoclax dose ramp-up will begin at Cycle 4. The combination of I+VEN will be given for 12 cycles (through Cycle 15). Subjects randomly assigned to Treatment Arm B (G-Clb) will receive G-Clb for 6 cycles. An independent Data Monitoring Committee (DMC) for safety review will be formed and constituted according to regulatory agency guidelines (see Section 11.9). Subjects who are eligible and choose to participate in the Subsequent Therapy Phase will receive subsequent single-agent ibrutinib until disease progression or unacceptable toxicity.

Subject participation will include a Screening Phase, a Treatment Phase, and a Follow-up Phase. The Screening Phase will be for a period of 30 days before randomization. The Treatment Phase will extend from randomization until study treatment discontinuation from fixed-duration treatment with I+VEN or G-Clb. The Follow-up Phase will begin once a subject discontinues treatment. Subjects who discontinue treatment for reasons other than disease progression in Treatment Phase will continue to have disease evaluations (DEs) according to Table 3. 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. Participation in this phase of the study is not mandatory and is based on investigator's discretion. The Follow-up Phase will continue until death, lost to follow-up, consent withdrawal, or study end, whichever occurs first. Subjects who discontinue treatment for reasons other than disease progression in the Subsequent Therapy Phase will continue to have DEs according to Table 4. The primary analysis and reporting of the study will be conducted after 71 PFS events have been observed after randomization. Study end is defined as approximately 5 years after the last subject is randomized into the study or after 50% of the subjects have died, whichever comes first. Subjects receiving single-agent ibrutinib in the Subsequent Therapy Phase may be offered participation in a separate study on or before the end of the current study to ensure continuity of ibrutinib therapy.

Assessment of disease response and progression will be conducted in accordance with the iwCLL 2008 Guidelines.[28] The investigator will evaluate sites of disease by physical examination and radiological imaging. The primary efficacy analysis of PFS will be based on the IRC assessment of PD in the intent-to-treat (ITT) population. Patient-reported health outcomes, functional status, and well-being will also be measured.

During the study, safety evaluations will include AE monitoring, physical examinations, review of concomitant medications, and evaluation of clinical laboratory parameters (hematology and chemistry). At each site visit, subjects will be assessed for toxicity. Blood samples will be drawn for pharmacokinetic (Treatment Arm A only) and biomarker studies. All study evaluations will be conducted per the Time and Events Schedule that corresponds to the assigned treatment arm (Table 1 for Treatment Arm A, Table 2 for Treatment Arm B, Table 3 for DEs, and Table 4 for the Subsequent Therapy Phase).

3.2. Study Design Rationale

This is a Phase 3, randomized study evaluating the combination I+VEN compared with the standard of care G-Clb, in the first-line treatment of subjects with CLL. The study will recruit subjects globally and is adequately powered to demonstrate an improvement in PFS with the I+VEN combination over the standard of care. This study design is widely employed to obtain data to support regulatory applications for new treatments.

Randomization will be used to minimize bias in the assignment of subjects to treatment groups, to increase the likelihood that known and unknown subject attributes (eg, demographic and baseline characteristics) are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups. Subjects will be stratified by *IGHV* mutational status (mutated vs. unmutated vs. not available), a well-defined prognostic indicator for patients with CLL, and presence of del11q (yes vs. no).

The primary endpoint for the Phase 3 Study CLL3011 is independently reviewed PFS using the 2008 iwCLL guidelines, including recent clarifications.[26,27] Demonstration of an improvement in PFS is viewed as a clinical benefit and an acceptable primary endpoint for CLL. As such, it has served as the basis for regulatory approvals in CLL. The key secondary endpoints for this study include rate of MRD-negative remissions in the bone marrow, ORR, OS, and safety of the combination. The endpoints of rate of MRD-negative remission, ORR, and OS are well-defined and recommended endpoints for the evaluation of new treatments for CLL.

The trial involves a novel combination regimen given at a finite duration. Treatment with I+VEN is anticipated to lead to a lower rate of clonal evolution and resistance mutations. For this reason, blood and bone marrow samples will be collected at baseline and other prespecified timepoints to explore biomarkers predictive of response to and relapse following study treatment.

Subjects from either treatment arm who progress after I+VEN or G-Clb may become eligible to receive single-agent ibrutinib in the Subsequent Therapy Phase. Response data, as well as biomarker samples, will be collected to evaluate the efficacy of ibrutinib in subjects previously treated with I+VEN in a subsequent pooled analysis.

4. SUBJECT POPULATION

Screening for eligible subjects will be performed up to 30 days before randomization.

The inclusion and exclusion criteria for enrolling subjects in this study are described in the following 2 subsections. If there is a question about the inclusion or exclusion criteria, the investigator must consult with the appropriate sponsor representative and resolve any issues before enrolling a subject in the study. Waivers are not allowed.

Eligibility criteria for the Subsequent Therapy Phase are presented in Section 9.1.5.1.

For a discussion of the statistical considerations of subject selection, refer to Section 11.2, Sample Size Determination.

4.1. Inclusion Criteria

Each potential subject must satisfy all of the following criteria to be enrolled in the study:

1. Adult subjects who are:
   a. ≥65 years old or,
   b. 18 to 64 years old and have at least 1 of the following:
      1) CIRS score >6 (see Attachment 2)[48]
      2) Creatinine clearance (CrCl) estimated <70 mL/min using Cockcroft-Gault equation
2. Diagnosis of CLL or SLL that meets iwCLL criteria.[28,45]
3. Active CLL/SLL requiring treatment per the iwCLL criteria.[28]
   a. Evidence of progressive marrow failure as manifested by the development of, or worsening of, anemia or thrombocytopenia or both;
   b. Massive (ie, at least 6 cm below the left costal margin) or progressive or symptomatic splenomegaly;
   c. Massive nodes (ie, at least 10 cm in longest diameter) or progressive or symptomatic lymphadenopathy;
   d. Progressive lymphocytosis with an increase of more than 50% over a 2-month period or lymphocyte doubling time of less than 6 months;
   e. Constitutional symptoms, defined as 1 or more of the following:
      1) Unintentional weight loss ≥10% within the previous 6 months prior to the start of screening;
      2) Significant fatigue (inability to work or perform usual activities);
      3) Fevers higher than 100.5°F or 38.0°C for 2 or more weeks without evidence of infection;
      4) Night sweats for more than 1 month without evidence of infection.
4. Measurable nodal disease (by CT), defined as at least one lymph node >1.5 cm in longest diameter.

5. ECOG PS Grade ≤2.
6. Adequate organ function defined as follows:
    a. Absolute neutrophil count (ANC) ≥750 cells/µL independent of growth factor support;
    b. Platelets ≥50,000 cells/µL independent of transfusion support for at least 7 days prior to randomization;
    c. Hemoglobin >8.0 g/dL independent of transfusion support for at least 7 days prior to randomization;
    d. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤3.0 x upper limit of normal (ULN);
    e. Total bilirubin ≤1.5 x ULN (unless due to Gilbert's syndrome);
    f. Estimated CrCl ≥30 mL/min (Cockcroft-Gault equation).
7. Prothrombin time/international normalized ratio (INR) <1.5 x ULN and activated partial thromboplastin time (aPTT) <1.5 x ULN (unless abnormalities are unrelated to coagulopathy or bleeding disorder).
8. Woman of childbearing potential must have a negative, highly sensitive serum (β-human chorionic gonadotropin [β-hCG]) or urine pregnancy test at screening.
9. Women of childbearing potential must be practicing a highly effective, preferably user-independent method of birth control (failure rate of <1% per year when used consistently and correctly) during treatment with any drug in this study and for up to 1 month after the last dose of venetoclax, 3 months after last dose of ibrutinib, 6 months after the last dose of chlorambucil, and 18 months after last dose of obinutuzumab, consistent with local regulations regarding the use of birth control methods for subject participating in clinical studies. Women using hormonal contraceptives should add a barrier method.

    Examples of highly effective methods of contraception are located in Attachment 3, Contraceptive and Barrier Guidance and Collection of Pregnancy Information.
10. Women must agree not to donate eggs for the purpose of assisted reproduction during treatment and for 3 months after the last dose of ibrutinib and 1 month after the last dose of venetoclax, 6 months after the last dose of chlorambucil, and 18 months after last dose of obinutuzumab.
11. During treatment and for a minimum of 1 spermatogenesis cycle (defined as 90 days) after receiving the last dose of any study treatment, in addition to the user-independent highly effective method of contraception, a man
    a. who is sexually active with a woman of childbearing potential must agree to use a barrier method of contraception (eg, condom with spermicidal foam/gel/film/cream/suppository)
    b. who is sexually active with a woman who is pregnant must use a condom
    c. must agree not to donate sperm for the purpose of reproduction
12. Must sign an informed consent form (ICF) indicating that he or she understands the purpose of, and the procedures required for, the study. Subjects must be willing and able to adhere to the prohibitions and restrictions specified in this protocol.

4.2. Exclusion Criteria

Any potential subject who meets any of the following criteria will be excluded from participating in the study:

1. Prior anti-leukemic therapy for CLL or SLL.
2. Presence of del17p or known TP53 mutation detected at a threshold of >10% variable allele frequency (VAF).[40]
3. Major surgery within 4 weeks of first dose of study treatment. For definition of major surgery, see Section 4.3 or contact the medical monitor.
4. Known bleeding disorders (eg, von Willebrand's disease or hemophilia).
5. Central nervous system (CNS) involvement or suspected Richter's syndrome.
6. An individual organ/system impairment score of 4 as assessed by CIRS, except for the eyes, ears, nose, throat, and larynx system, limiting the ability to receive treatment in this study.[48]
7. Uncontrolled autoimmune hemolytic anemia or autoimmune thrombocytopenia (Coombs positivity in the absence of hemolysis is not an exclusion).
8. Chronic use of corticosteroids more than 20 mg/day of prednisone or its equivalent within 7 days of initiation of study treatment.
9. History of prior malignancy, except:
    a. Malignancy treated with curative intent and with no known active disease present for ≥24 months before randomization;
    b. Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease;
    c. Adequately treated cervical carcinoma in situ without evidence of disease;
    d. Malignancy, which is considered cured with minimal risk of recurrence.
10. Received live, attenuated vaccine within 4 weeks of randomization.
11. History of renal, neurologic, psychiatric, endocrinologic, metabolic, immunologic, or hepatic condition that in the opinion of the investigator would adversely affect a subject's participation in the study.
12. Currently active, clinically significant Child-Pugh Class B or C hepatic impairment according to the Child-Pugh classification (see Attachment 4 Child-Pugh classification).
13. Uncontrolled active systemic infection or any life-threatening illness, medical condition, or organ system dysfunction which, in the investigator's opinion, could compromise the subject's safety or put the study outcomes at undue risk.
14. Inability or difficulty swallowing capsules/tablets, malabsorption syndrome, or any disease or medical condition significantly affecting gastrointestinal function.
15. Stroke or intracranial hemorrhage within 6 months prior to randomization.

16. Active, clinically significant cardiovascular disease, such as uncontrolled arrhythmia or Class 3 or 4 congestive heart failure as defined by the New York Heart Association Functional Classification; or a history of myocardial infarction, unstable angina, or acute coronary syndrome within 6 months prior to randomization.
17. Anticoagulation with warfarin or equivalent vitamin K antagonists (eg, phenprocoumon) or ongoing treatment with agents known to be strong cytochrome (CYP) P450 3A inhibitors.
18. Positive test for HIV by history or at screening.
19. Subjects who are positive for Hepatitis B core antibody, Hepatitis B surface antigen, or Hepatitis C antibody must have a negative PCR result before enrollment. Those who are PCR positive will be excluded.
20. Known allergy to either xanthine oxidase inhibitors or rasburicase.
21. Female subjects who are pregnant, breastfeeding, or planning to become pregnant while enrolled in this study or up to 1 month after the last dose of venetoclax, 3 months of last dose of ibrutinib, 6 months after the last dose of chlorambucil, or 18 months after last dose of obinutuzumab.
22. Male subjects who plan to father a child while enrolled in this study or within 90 days after the last dose of any study treatment.
23. Known hereditary galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption.
24. Any contraindication to one of the study medications including hypersensitivity to the active substance or to any of the excipients of ibrutinib, venetoclax, obinutuzumab, or chlorambucil.

NOTE: Investigators should ensure that all study enrollment criteria have been met at screening. If a subject's clinical status changes after screening (based on available laboratory results or receipt of additional medical records), but before the first dose of study treatment such that he or she no longer meets all eligibility criteria, the subject should be excluded from participation in the study. Section 17.4, Source Documentation, describes the required documentation to support meeting the enrollment criteria.

4.3. Prohibitions and Restrictions

Potential subjects must adhere to the following prohibitions and restrictions during the study. Subjects on I+VEN should avoid consumption of foods or beverages containing grapefruit, Seville oranges, and starfruit (carambola) as these inhibit CYP3A4/5 and alter drug metabolism. Precautions with concomitant medications and prohibited medications are detailed in Sections 8.2 and 8.3, respectively.

The following guidance should be applied during the perioperative period for subjects who require surgical intervention or an invasive procedure while receiving ibrutinib:

- For major surgical procedures, including any surgery or invasive procedure requiring sutures or staples for closure, ibrutinib should be held at least 7 days prior to the intervention and at least 7 days after the procedure, and restarted at the discretion of the investigator, when the

surgical site is reasonably healed without serosanguineous drainage or the need for drainage tubes.

- For minor procedures (such as a central line placement, needle biopsy, thoracentesis, or paracentesis), ibrutinib should be held for at least 3 days prior to the procedure and should not be restarted for at least 3 days after the procedure. For bone marrow biopsies that are performed while the subject is on study medication, it is not necessary to hold the study medications.
- For emergency procedures, all study treatments should be held after the procedure until the surgical site is reasonably healed, for at least 7 days after the urgent surgical procedure.

5. TREATMENT ALLOCATION

Treatment Allocation

Procedures for Randomization and Stratification

Central randomization will be implemented in this study for the Treatment Phase. Subjects will be randomly assigned to 1 of 2 treatment groups based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor. The randomization will be balanced by using permuted block and will be stratified by *IGHV* mutational status (mutated vs. unmutated vs. not available) and presence of del11q (yes vs. no). The interactive web response system (IWRS) will assign a unique intervention code, which will dictate the intervention assignment and matching study intervention kit for the subject. The requestor must use his or her own user identification and personal identification number when contacting the IWRS and will then give the relevant subject details to uniquely identify the subject.

6. DOSAGE AND ADMINISTRATION

Subjects will be randomly assigned 1:1 to receive I+VEN (Treatment Arm A; see Section 6.1) or G-Clb (Treatment Arm B; see Section 6.2) in the Treatment Phase. Eligible subjects who participate in the Subsequent Therapy Phase will receive single-agent ibrutinib (see Section 6.3).

6.1. Treatment Arm A (Ibrutinib plus Venetoclax) Administration

Subjects randomly assigned to Treatment Arm A (I+VEN) will receive ibrutinib (420 mg/day orally) given as lead-in treatment for 3 cycles. Starting at Cycle 4 and contingent on completion of TLS risk assessment (see Section 6.1.2.2), venetoclax dose ramp-up (from 20 to 400 mg over 5 weeks) will begin, and venetoclax will be administered with ibrutinib for 12 cycles through Cycle 15.

6.1.1. Ibrutinib

6.1.1.1. Dosage and Administration

Ibrutinib 420 mg (3 x 140 mg capsules) is administered orally once daily, starting at Cycle 1, Day 1. The capsules are to be taken around the same time each day with a glass of water. The capsules should be swallowed whole with water and should not be opened, broken, or chewed.

During cycles with venetoclax combination dosing, ibrutinib and venetoclax should be taken together at the same time, with a glass of water and a meal. If a dose of ibrutinib is missed, it can be taken as soon as possible on the same day with a return to the normal schedule the following day. The subject should not take extra capsules to make up the missed dose.

At any given visit, sufficient study medication required for treatment until the next visit should be dispensed. Unused study medication dispensed during previous visits must be returned and drug accountability records will be updated. Returned capsules cannot be re-used in this study or outside the study. Study staff will instruct subjects on how to store medication for at-home use as indicated for this protocol.

6.1.1.2. Ibrutinib Dose Modification

Treatment with ibrutinib should be temporarily stopped for unmanageable, potentially ibrutinib-related toxicity that is Grade ≥3 in severity. Ibrutinib may be temporarily stopped for a maximum of 28 consecutive days. Ibrutinib should be discontinued permanently in the event of a toxicity lasting more than 28 days, unless continued treatment is approved by the sponsor.

The dose of ibrutinib must be modified according to the dose modification guidance in Table 7 if any of the following potentially drug-related toxicities occur:

- ANC <500 cells/µL for more than 7 days. See Section 8.1 for instructions regarding the use of growth factor support.
- Platelets <50,000 cells/µL in the presence of clinically significant bleeding.
- Platelets <25,000 cells/µL.
- Grade 3 nausea or Grade 3 or 4 vomiting or Grade 3 or 4 diarrhea, if persistent despite optimal anti-emetic or anti-diarrheal therapy.
- Any other Grade 4 or unmanageable Grade 3 toxicity.

If the dose of ibrutinib is reduced, the dose of ibrutinib may be re-escalated at investigator's discretion after 2 dose-reduced cycles in the absence of a recurrence of the toxicity that led to the reduction. No dose escalation of ibrutinib above 420 mg is allowed in this study. Dose changes must be recorded in the Dose Administration electronic case report form (eCRF).

Table 7: Ibrutinib Dose Modifications

Occurrence	Action to be Taken
First	Withhold ibrutinib until recovery to Grade ≤1 or baseline; may restart at original dose level
Second	Withhold ibrutinib until recovery to Grade ≤1 or baseline; may restart at 1 dose level lower (ie, 280 mg/day dose)
Third	Withhold ibrutinib until recovery to Grade ≤1 or baseline; may restart at 1 dose level lower (ie, 140 mg/day dose)
Fourth	Discontinue study drug

Note: For hematologic toxicities, restart of ibrutinib may be considered once the toxicity has resolved to study entry criteria level or better.

For dose modification during concomitant treatment with CYP3A inhibitors refer to Attachment 9.

During cycles with venetoclax combination dosing, the decision to dose modify a study drug due to a toxicity will be based on the investigator attribution of relatedness to a given drug. For example, if an AE occurs and is considered related to venetoclax but not ibrutinib, the dose of venetoclax should be modified while ibrutinib should remain the same. If the AE is considered potentially related to both drugs, adjusting the dose of venetoclax before ibrutinib is the recommended first action, taking into consideration the possibility of higher systemic exposure of venetoclax when administered in combination with ibrutinib. For cases where the investigator is uncertain of what action to take, the study monitor may be contacted for further discussion.

If ibrutinib is discontinued for toxicity, then treatment with venetoclax may be continued.

6.1.1.2.1. Ibrutinib Dose Modification for Subjects With Hepatic Impairment

Ibrutinib is metabolized in the liver. Therefore, subjects with clinically significant hepatic impairment at the time of screening (Child-Pugh Class B or C) are excluded from study participation. For subjects who develop mild liver impairment while on study (Child-Pugh Class A), the recommended dose reduction for ibrutinib is to a level of 280 mg daily. For subjects who develop moderate liver impairment while on study (Child-Pugh Class B), the recommended dose reduction is to a level of 140 mg daily. For subjects who develop severe hepatic impairment (Child-Pugh Class C), ibrutinib must be held until resolved to moderate impairment (Child-Pugh Class B) or better. Monitor subjects for signs of toxicity and follow dose modification guidance as needed (see Attachment 4 for Child-Pugh classification).

6.1.2. Venetoclax

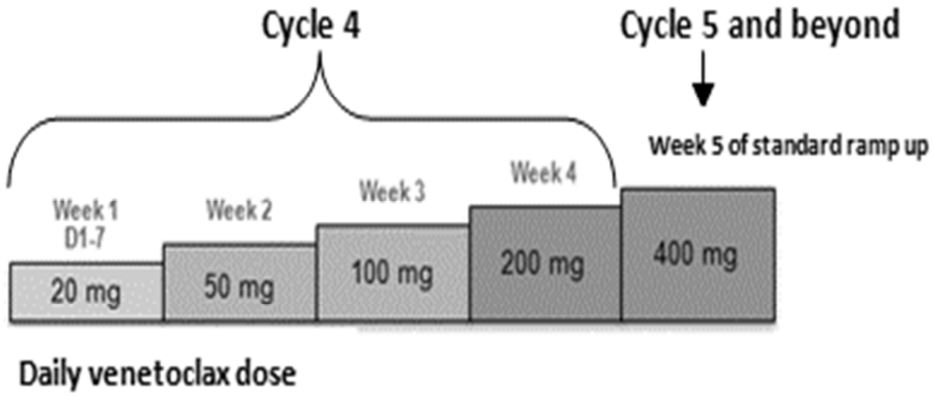
For full details of the warnings, precautions and AEs associated with treatment with venetoclax, please refer to the product label.[54]

6.1.2.1. Dosage and Administration

Venetoclax tablets should be taken orally once daily with a meal and water around the same time each day. Venetoclax tablets should be swallowed whole and not chewed, crushed, or broken prior to swallowing. During cycles with ibrutinib combination dosing, ibrutinib and venetoclax should be taken together at the same time. If a subject misses a dose of venetoclax within 8 hours of the time it is usually taken, the subject should take the missed dose as soon as possible on the same day. If a subject misses a dose of venetoclax by more than 8 hours, the subject should not take the missed dose and should resume the usual dosing schedule the following day. If a subject vomits following dosing, no additional dose should be taken that day. The next prescribed dose should be taken at the usual time the following day.

The starting dose is 20 mg of venetoclax once daily for 7 days. The dose must be gradually increased over a period of 5 weeks up to the recommended daily dose of 400 mg as shown in Figure 3.

Figure 3: Venetoclax Dose Ramp-up



The 5-week dose-titration schedule is designed to gradually reduce tumor burden (debulk) and decrease the risk of TLS.

The first dose of venetoclax will be delivered in the clinic (or in the hospital depending on TLS risk category) on Cycle 4 Day 1. Dose escalation will occur in accordance with specific risk-based TLS prophylaxis and monitoring measures that may include dose delays or dose reductions. After completion of the 5-week dose ramp-up, subsequent dosing is typically continued on an outpatient basis.

6.1.2.2. Prophylaxis and Management of Tumor Lysis Syndrome

Venetoclax may cause a rapid reduction in tumor burden and thus poses a risk for TLS in the initial 5-week ramp-up phase. Changes in electrolytes consistent with TLS that require prompt management may occur as early as 6 to 8 hours following the first dose of venetoclax and at each dose increase. The risk of TLS is a continuum based on multiple factors, including tumor burden and comorbidities (Table 8). Subjects with high tumor burden are at a greater risk of TLS when initiating venetoclax. Reduced renal function further increases the risk. The risk may decrease as tumor burden decreases with treatment.

Prior to initiating venetoclax, tumor burden assessment, including radiographic evaluation (eg, CT scan), must be performed for all subjects. Blood chemistry (potassium, uric acid, phosphorus, calcium, and creatinine) must be assessed as per the Time and Events Schedules and pre-existing abnormalities must be corrected. The prophylaxis measures listed below must be followed. More intensive measures should be employed as risk increases.

In all subjects, assess subject-specific factors for level of risk of TLS and provide prophylactic hydration and anti-hyperuricemics to subjects prior to the first dose of venetoclax to reduce the risk of TLS. Employ more intensive measures (intravenous hydration, frequent monitoring, and hospitalization) as risk increases.

Subjects with baseline CrCl ≤50 mL/min or with high risk for TLS as defined by at least one lesion ≥10 cm, or at least one lesion ≥5 cm plus circulating lymphocytes >25,000 cells/µL, should be hospitalized during the first 24 to 48 hours of treatment with 20 mg and 50 mg of venetoclax for TLS monitoring and intravenous hydration. Hospitalization should be considered for subjects who are at low or medium risk of TLS if they do not have immediate access to a facility capable of correcting TLS promptly, or are otherwise considered at risk for TLS.

Table 8: TLS Prophylaxis Based on Tumor Burden from Clinical Trial Data (consider all comorbidities before final determination of prophylaxis and monitoring schedule)

Tumor Burden		Prophylaxis		Blood Chemistry Monitoring[c,d]
		Hydration[a]	Anti-hyperuricemics	Setting and Frequency of Assessments
Low	All LN <5 cm AND ALC <25 x10^9/L	Oral (1.5-2 L)/daily	Allopurinol[b]	Outpatient • Predose, 6 to 8 hours, 24 hours at first dose of 20 mg and 50 mg • Predose at subsequent ramp-up doses
Medium	Any LN 5 cm to <10 cm OR ALC ≥25 x10^9/L	Oral (1.5-2 L)/daily and consider additional intravenous	Allopurinol[b]	Outpatient • Predose, 6 to 8 hours and 24 hours at first dose of 20 mg and 50 mg • Predose at subsequent ramp-up doses • Consider hospitalization for subjects with CrCl <80mL/min at first dose of 20 mg and 50 mg; see below for monitoring in hospital
High	Any LN ≥10 cm OR ALC ≥25 x10^9/L AND any LN ≥5 cm	Oral (1.5-2 L)/daily and intravenous (150-200 mL/hr as tolerated)	Allopurinol[b]; consider rasburicase if baseline uric acid is elevated	In hospital at first dose of 20 mg and 50 mg • Predose, 4, 8,12 and 24 hours Outpatient at subsequent ramp-up doses • Predose, 6 to 8, and 24 hours
	Any LN size or ALC AND CrCl ≤50 mL/min			

Abbreviations: ALC=absolute lymphocyte count; CrCL=creatinine clearance; LN=lymph node; TLS=tumor lysis syndrome.

a. Start oral hydration 2 days prior to the initiation of venetoclax. Administer intravenous hydration for any subject who cannot tolerate oral hydration.
b. Start allopurinol or xanthine oxidase inhibitor 2 to 3 days prior to initiation of venetoclax.
c. Evaluate blood chemistries (potassium, uric acid, phosphorus, calcium, and creatinine); review in real time.
d. For subjects at risk of TLS, monitor blood chemistries at 6 to 8 hours and at 24 hours with each subsequent ramp-up dose.

See Attachment 6 for recommendations for initial management of electrolyte abnormalities and prevention of TLS.

6.1.2.3. Venetoclax Dose Modification

See Table 9 for dose modifications for toxicities related to venetoclax. For subjects who have had a dosing interruption greater than 1 week during the first 5 weeks of ramp-up phase or greater than 2 weeks when at the daily dose of 400 mg, reassess for risk of TLS to determine if re-initiation with a reduced dose is necessary (eg, all or some levels of the dose ramp-up schedule). During the ramp-up phase, continue the reduced dose for 1 week before increasing the dose. Consider discontinuing venetoclax for subjects who require dose reductions to less than 100 mg for more than 2 weeks.

Table 9: Venetoclax Recommended Dose Modifications for Toxicities

Event	Occurrence	Action
Tumor Lysis Syndrome		
Blood chemistry changes or symptoms suggestive of TLS (see Howard Criteria in Attachment 7)	Any	Withhold the next day's dose. If resolved within 24-48 hours of last dose, resume at the same dose.
		For any blood chemistry changes requiring more than 48 hours to resolve, resume at a reduced dose (see Table 10).
		For any events of clinical TLS[a], resume at a reduced dose following resolution (see Table 10).
Non-Hematologic Toxicities		
Grade 3 or 4 non-hematologic toxicities	1st occurrence	Withhold venetoclax Once the toxicity has resolved to Grade 1 or baseline level, venetoclax therapy may be resumed at the same dose. No dose modification is required.
	2nd and subsequent occurrences	Withhold venetoclax. Follow dose reduction guidelines in Table 10 when resuming treatment with venetoclax after resolution. A larger dose reduction may occur at the discretion of the investigator.
Hematologic Toxicities		
ANC <1000/µL with infection or fever; ANC < 500/µL Platelet <25,000/µL Hb <8g/dL	1st occurrence	Withhold venetoclax. To reduce the infection risks associated with neutropenia, G-CSF may be administered with venetoclax if clinically indicated. Once the toxicity has resolved to study entry criteria level or better, venetoclax therapy may be resumed at the same dose.
	2nd and subsequent occurrence	Withhold venetoclax. Consider using G-CSF as clinically indicated. Follow dose reduction guidelines in Table 10 when resuming treatment with venetoclax after resolution. Additional dose reductions may occur at the discretion of the physician.

Abbreviations: ANC=absolute neutrophil count; G-CSF=granulocyte-colony stimulating factor; Hb=hemoglobin; TLS=tumor lysis syndrome

[a] Clinical TLS was defined as laboratory TLS with clinical consequences such as acute renal failure, cardiac arrhythmias, or sudden death and/or seizures.

Table 10: Dose Modification for Toxicity during Venetoclax Treatment	
Dose at Interruption, mg	**Restart Dose, mg[a]**
400	300
300	200
200	100
100	50
50	20
20	10

[a] During the dose-titration phase, continue the reduced dose for 1 week before increasing the dose.

Use of strong CYP3A inhibitors is contraindicated during venetoclax initiation and dose ramp-up. For dose modification during concomitant treatment with CYP3A inhibitors refer to Attachment 9.

During cycles with I+VEN combination dosing, the decision to dose modify a study drug due to a toxicity will be based on the investigator attribution of relatedness to a given drug. For example, if an AE occurs and is considered related to venetoclax but not ibrutinib, the dose of venetoclax should be modified while ibrutinib should remain the same. If the AE is considered potentially related to both drugs, adjusting the dose of venetoclax before ibrutinib is the recommended first action, taking into consideration the possibility of higher systemic exposure of venetoclax when administered in combination with ibrutinib. For cases where the investigator is uncertain of what action to take, the study monitor may be contacted for further discussion.

If venetoclax is discontinued for toxicity, then treatment with ibrutinib may be continued.

6.2. Treatment Arm B (Chlorambucil plus Obinutuzumab) Administration

Subjects randomly assigned to Treatment Arm B will receive 6 cycles (each cycle is defined as 28 days) of G-Clb treatment in the absence of disease progression or treatment-limiting toxicity, as shown below. Obinutuzumab infusions will be administered in clinic as described in Section 6.2.1. Chlorambucil will be given in clinic on days that coincide with obinutuzumab infusions. On days in which chlorambucil is administered alone, it may be given in clinic or issued to the subject for home administration, as described in Section 6.2.2.1.

- Obinutuzumab, 1000 mg infused IV on Days 1, 8 and 15 of Cycle 1, and on Day 1 of Cycles 2 to 6
- Chlorambucil, 0.5 mg/kg body weight, on Days 1 and 15 of Cycles 1 to 6

6.2.1. Obinutuzumab

For full details of the warnings, precautions and AEs associated with treatment with obinutuzumab, please refer to the product label.[22]

6.2.1.1. Obinutuzumab Dosage and Administration

Each dose of obinutuzumab is 1000 mg administered intravenously, per institutional standards, with the exception of the first infusion in Cycle 1 (Table 11). It is recommended that the initial 1000 mg dose be administered over Day 1 (100 mg) and Day 2 (900 mg). For subjects who tolerate the initial 100 mg dose well and required no dose interruption or modification of the infusion rate, the treating physician may opt to administer the remaining 900 mg on Day 1. Obinutuzumab should be administered according to the following schedule:

Table 11: Obinutuzumab Dosing Schedule

Day of Treatment Cycle		Dose of Obinutuzumab	Rate of infusion (in the absence of infusion reactions/hypersensitivity during previous infusions)
Cycle 1	Day 1	100 mg	Administer at 25 mg/hr over 4 hours. Do not increase the infusion rate.
	Day 2 (or Day 1 continued)	900 mg	Administer at 50 mg/hr. The rate of the infusion may be escalated in increments of 50 mg/hr every 30 minutes to a maximum rate of 400 mg/hr.
	Day 8	1000 mg	If no infusion reaction during the previous infusion and the final rate was 100 mg/hr or faster, infusions may be started at a rate of 100 mg/hr and increased by 100 mg/hr increments every 30 minutes to a maximum of 400 mg/hr.
	Day 15	1000 mg	
Cycle 2-6	Day 1	1000 mg	

If a planned dose of obinutuzumab is missed, it should be administered as soon as possible; do not wait until the next planned dose. The planned treatment interval should be maintained between doses. If appropriate, subjects who do not complete the Day 1 Cycle 1 dose may proceed to the Day 2 Cycle 1 dose.

6.2.1.1.1. Obinutuzumab Premedication

Premedication for infusion-related reactions (IRRs) and TLS is recommended; please see Attachment 8 for details regarding management of these risks.

6.2.1.2. Obinutuzumab Dose Delays and Modifications

6.2.1.2.1. Infusion Reactions

Medical management (eg, glucocorticoids, epinephrine, bronchodilators, and/or oxygen) should be provided for infusion reactions as needed. Subjects should be closely monitored during the entire infusion. Note that infusion reactions within 24 hours of receiving obinutuzumab have occurred. If a subject experiences an infusion reaction of any grade during infusion, adjust the infusion as follows:

- Grade 4 (life-threatening): For any Grade 4 infusion reaction, including anaphylaxis and acute life-threatening respiratory symptoms, stop infusion immediately and permanently discontinue obinutuzumab therapy.

- Grade 3 (severe): Interrupt infusion and manage symptoms. Upon resolution of symptoms, consider restarting obinutuzumab infusion at no more than half the previous rate (the rate being used at the time that the infusion reaction occurred) and, if subject does not experience any further infusion reaction symptoms, infusion rate escalation may resume at the increments and intervals as appropriate for the treatment dose (Table 11). Permanently discontinue treatment if subject experience a Grade 3 infusion-related symptom at rechallenge. Cycle 1 Day 1 infusion rate may be increased back up to 25 mg/hr after 1 hour, but not increased further.
- Grade 1 to 2 (mild to moderate): Reduce infusion rate or interrupt infusion and treat symptoms. Upon resolution of symptoms, continue or resume infusion and, if subject does not experience any further infusion reaction symptoms, infusion rate escalation may resume at the increments and intervals as appropriate for the treatment dose (Table 11). Cycle 1 Day 1 infusion rate may be increased back up to 25 mg/hr after 1 hour, but not increased further.

If the previous infusion rate was not well tolerated, instructions for the infusion rate of Cycle 1 Days 1 and 2 should be used for subsequent cycles.

6.2.1.2.2. Obinutuzumab Dose Delays

There will be no dose reductions for obinutuzumab. Obinutuzumab should be withheld for any unmanageable, potentially obinutuzumab-related toxicity that merits a dose delay in the opinion of the investigator. This includes active infections, severe or life-threatening cytopenia, or a Grade ≥2 non-hematologic toxicity. Obinutuzumab therapy should be withheld until toxicity has resolved to study entry criteria level or better for hematologic toxicities or at least Grade 1 for non-hematologic toxicities. In certain circumstances, therapy with obinutuzumab may be re-initiated despite an ongoing toxicity which has not resolved to Grade ≤1, provided it is clinically appropriate in the opinion of the investigator and it has been discussed with the medical monitor.

Investigators should refer to the current obinutuzumab package insert for a comprehensive list of potential adverse reactions,[22] their prophylaxis and management. Particular attention should be paid to the Warnings and Precautions sections. Obinutuzumab may cause severe and life-threatening infusion reactions. Management of infusion reactions may require temporary interruptions, reductions in the rate of infusion, or treatment discontinuation. TLS has also been observed in patients treated with obinutuzumab and should be managed in accordance with the package insert.[22]

Obinutuzumab may be held for a maximum of 28 days due to toxicity. Obinutuzumab treatment should be discontinued in the event of a toxicity lasting >28 days, unless discussed with and approved by the medical monitor. If obinutuzumab is discontinued due to toxicity, then treatment with chlorambucil may be continued.

6.2.2. Chlorambucil

For full details of the warnings, precautions and AEs associated with treatment with chlorambucil, please refer to the product label.[39]

6.2.2.1. Chlorambucil Dosage and Administration

Chlorambucil will be administered orally at a dose of 0.5 mg/kg body weight, on Days 1 and 15 of Cycles 1 to 6 (each of 28-day duration). Chlorambucil tablets should be taken on an empty stomach (at least one hour before meals or 3 hours after meals).

On Day 1 and Day 15 of Cycle 1, and on Day 1 of Cycles 2 to 6, chlorambucil will be given in clinic after the required serum chemistry and hematology testing has been completed and the results assessed by the treating physician. Chlorambucil for Day 15 of Cycles 2 to 6 may be issued to the subject for home administration during the Day 1 clinic visit for each respective cycle. Subjects must be advised to await instructions from the treating physician before taking the Day 15 dose of chlorambucil at home. Predose serum chemistry and hematology testing must be completed and the results assessed by the treating physician before each Day 15 dose of chlorambucil. However, these may be done outside the treating institution.

6.2.2.2. Chlorambucil Dose Modifications

The guidelines for chlorambucil dose reductions are described in Table 12. A dose delay of up to 28 days is permitted for chlorambucil. If the treatment is delayed for more than 28 days, chlorambucil should be discontinued. If severe or life-threatening cytopenia listed prevents treatment on Day 15 of any cycle, the Day 15 chlorambucil dose should be skipped. Chlorambucil administration on Day 1 of the following cycle will be given if the cytopenia resolves to Grade ≤2. If the cytopenia persists, chlorambucil administration should be delayed until the cytopenia improves to Grade ≤2.

Table 12: Dose Modification for Chlorambucil Due to Toxicity

Toxicity	Chlorambucil Dose Action

Cytopenia defined as one of the following:
• ANC <500/µL for ≥7 days
• Platelet count <50,000/µL with bleeding
• Platelet count <25,000/µL
• Hgb <8.0 g/dL
	• Delay dosing for a maximum of 4 weeks
	• 1st episode
	  ○ Hold until recovery to study entry criteria levels or better
	  ○ Decrease dose to 75% of initial dose
	• 2nd episode
	  ○ Hold until recovery to study entry criteria levels or better
	  ○ Decrease dose to 50% of initial dose
	• 3rd episode
	  ○ Discontinue chlorambucil

Grade 3 or 4 unmanageable, non-hematologic toxicity potentially related to study drug	• Delay dosing for a maximum of 4 weeks
	• 1st episode
	  ○ Hold until recovery to Grade ≤2
	  ○ Decrease dose to 75% of initial dose
	• 2nd episode
	  ○ Hold until recovery to Grade ≤2
	  ○ Decrease dose to 50% of initial dose
	• 3rd episode
	  ○ Discontinue chlorambucil

If chlorambucil is discontinued due to toxicity, then treatment with obinutuzumab may be continued.

6.3. Subsequent Therapy with Single-agent Ibrutinib

Ibrutinib 420 mg (3 × 140 mg capsules) will be administered orally once daily, starting at Cycle 1 Day 1 in the Subsequent Therapy Phase.

For subjects randomized to Treatment Arm A who received ibrutinib at a reduced dose, single-agent ibrutinib may be started at the previously tolerated dose and re-escalated to the full dose per investigator's discretion.

Guidelines for ibrutinib administration are provided in Section 6.1.1.

7. INTERVENTION COMPLIANCE

The investigator or designated study personnel will maintain a log of all study drugs dispensed and returned. Drug supplies for each subject will be inventoried and accounted for throughout the study.

The study drugs are to be prescribed only by the principal investigator or a qualified physician listed as a sub-investigator on required forms. Records should be kept on the study drug accountability form provided by the sponsor or its designee (any alternative forms must be preapproved by the sponsor). Further instructions regarding accountability for study drugs are provided in the Site Investigational Product Procedures Manual (SIPPM). Administration of the study drugs must be recorded in the subject's source documentation. The study drugs may not be used for any purpose other than that outlined in this protocol, including other human studies, animal investigations, or in vitro testing.

Instructions for proper self-administration and study drug storage conditions for at-home use will be provided. Precautions associated with the use of the study drugs and prohibited/restricted concomitant medications will be reviewed. The investigator or designated study site personnel will be responsible for providing additional instruction to any subject who is not compliant with taking the study drugs. In the absence of toxicity, if the dosing compliance is not 100%, then investigators or designated study site personnel should re-instruct subjects regarding proper dosing procedures, and the subject may continue study treatment.

8. CONCOMITANT THERAPY

Relevant concomitant therapies must be recorded throughout the study beginning with the time of written informed consent to 30 days after the last dose of study treatment or until the start of subsequent anti-leukemic therapy, whichever is first. Similarly, for subjects who are eligible to and who receive single-agent ibrutinib in the Subsequent Therapy Phase, concomitant therapies must be recorded at the time of the first dose and up to 30 days after the last dose of ibrutinib. Relevant concomitant therapies include drugs that are given for active medical conditions reported in the subject's medical history and treatments instituted for a reported AE/SAE. In most cases, drugs under the following categories need not be reported: nutritional supplements

(eg, multivitamins); prophylactic antiemetics and antinauseants; antiseptics and disinfectants; contrast media; emollients and protectives (eg, moisturizers); ophthalmologics and otologics; vaccines; sex hormones for contraception; and dermatologics.

The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

8.1. Permitted Concomitant Medications

The subject should receive supportive care during study participation, including fluids and electrolyte replacement, and antibiotics when appropriate. Use of neutrophil growth factors (filgastrim and pegfilgrastim) or red blood cell growth factors is permitted per the American Society of Clinical Oncology guidelines or per the institution's guidelines.[41] Transfusions may be given in accordance with institutional policy. Use of anti-microbial prophylaxis (eg, *Pneumocystis jirovecii* pneumonia prophylaxis with sulfamethoxazole and trimethoprim or equivalent), per the institution's guidelines, is recommended.

Short courses (<14 days) of corticosteroids for non-cancer related medical reasons (eg, joint inflammation, asthma exacerbation, and IRRs) are permitted at doses not exceeding 100 mg/day of prednisone or its equivalent. Treatment for autoimmune cytopenias is permitted for <14 days at doses that do not exceed 100 mg/day of prednisone or its equivalent.

8.2. Medications to be Used with Caution

- Drugs that may alter ibrutinib or venetoclax plasma concentrations (eg, strong and moderate CYP3A inhibitors/inducers (Attachment 5). Guidance on the use of these CYP3A inhibitors/inducers and required dose adjustments of ibrutinib and venetoclax are provided in Attachment 9. Note: Further information regarding the use of strong CYP3A inhibitors during venetoclax administration is provided in Section 8.3.
- Drugs that may have their plasma concentration altered by ibrutinib or venetoclax (eg, narrow therapeutic index P-glycoprotein [P-gp] substrates such as digoxin [Attachment 9])
- Antiplatelet agents and anticoagulants (Attachment 9)

8.3. Prohibited Concomitant Medications

Any non-study anti-leukemic therapy, including but not limited to chemotherapy, anticancer immunotherapy, small molecule targeted therapy, experimental therapy, or radiotherapy, is prohibited until disease progression has occurred. Localized, hormonal, or bone sparing treatment for non-B-cell malignancies and localized radiotherapy for medical conditions other than the underlying B-cell malignancies may be considered with approval of the medical monitor.

- Live vaccines must not be administered during study treatment phases but may be considered in the Follow-up Phase after B-cell recovery and approval of the medical monitor.

- Use of strong CYP3A inhibitors is contraindicated during venetoclax initiation and dose ramp up (Attachment 9).
- Corticosteroids at dosages equivalent to prednisone >20 mg/day for >14 days are prohibited until disease progression has occurred (refer to Section 8.1 for exceptions and further guidance).
- Warfarin or other vitamin K antagonists should not be administered concomitantly with ibrutinib (Attachment 9).

9. STUDY EVALUATIONS

9.1. Study Procedures

9.1.1. Overview

The study is divided into a Screening Phase, a Treatment Phase (Treatment Arm A [I+VEN]) or Treatment Arm B [G-Clb]), and a Follow-up Phase. Eligible subjects may also participate in a Subsequent Therapy Phase. The Time and Events Schedules (Table 1, Table 2, Table 3 and Table 4) summarize the frequency and timing of efficacy, PRO, biomarker, and safety measurements applicable to this study.

All visit-specific PRO assessments should be conducted before any tests, procedures, or other consultations for that visit, to prevent influencing subject perceptions. PRO assessments will be captured electronically.

Adverse event information will be collected using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 4.03. A separate toxicity scale (iwCLL grading scale for hematological toxicity in CLL studies) should be used to assess the severity of cytopenias (ie, neutropenia, anemia, thrombocytopenia, see Table 14).

Additional serum or urine pregnancy tests may be performed, as necessary, or as required by local regulation, to establish the absence of pregnancy at any time during the subject's participation in the study.

For each subject, the maximum amount of blood drawn will not normally exceed that typically required for medical management of this patient population. Repeat or unscheduled blood sampling may be taken for safety reasons or technical issues.

9.1.2. Screening Phase

Screening procedures will be performed up to 30 days before randomization. All subjects must sign an ICF prior to the conduct of any study-related procedures. During the Screening Phase, eligibility criteria will be reviewed and a complete clinical evaluation will be performed as specified in the respective Time and Events Schedules. This evaluation will include a complete medical history, confirmation of CLL diagnosis, staging at study entry (Attachment 10), and laboratory tests. Pathology reports, including fluorescence in situ hybridization (FISH) analysis for del17p and del11q, will be collected for sponsor review. Subjects with known presence of *TP53* mutations detected at a threshold of >10% VAF will be excluded from the study.[40] Results

from central *IGHV* testing and local del11q testing will be used for stratification and must be available prior to randomization. In addition, eCRFs relevant for evaluation of inclusion and exclusion provisions must be completed before IWRS approval for randomization is issued.

The collection of AEs and concomitant medications will commence after the study informed consent is signed. For women of childbearing potential, a urine or serum β-hCG pregnancy test will be performed. Clinical assessments performed as part of the subject's routine clinical evaluation and not specifically for this study need not be repeated after signed informed consent has been obtained provided the assessments fulfill the study requirements and are performed within the specified timeframe prior to randomization.

Evaluation for disease-related symptoms, a full physical examination, a complete blood count (CBC), and CT scans (or magnetic resonance imaging [MRI; Section 9.2.1.1]) are anticipated components of DE. Results of radiologic assessments obtained prior to signing the informed consent may be used if performed within 60 days of randomization, if the Imaging Acquisition Guidelines standards are met. Subsequent radiologic assessments performed throughout the study must be of the same modality as performed during screening. A bone marrow evaluation is required, preferably within 30 days of randomization; however, results within 90 days of randomization are acceptable. Bone marrow biopsies should be evaluated locally for morphology. Bone marrow aspirate or peripheral blood may be used to assess the subject's cytogenetic profile using standard CLL FISH probes to detect abnormalities in chromosomes 17, 13, 12, and 11. In addition, immunophenotyping should be performed on the aspirate or blood sample. Results will be collected in the eCRF. For subjects with SLL, a lymph node biopsy may be used for immunophenotyping, morphology, and FISH testing. For subjects undergoing a bone marrow biopsy and aspirate during the screening, a sample of the aspirate and biopsy should be collected for biomarker assays and MRD testing. Archived bone marrow slides for biomarkers are acceptable.

9.1.3. Open-label Treatment Phase

The Treatment Phase will begin at randomization and will continue until disease progression, unacceptable toxicity, or other reasons as described in Section 10. Subjects should start study treatment within 72 hours after randomization. The results of laboratory testing taken on Cycle 1 Day 1 of study treatment will be defined as the baseline values for safety assessments and treatment decisions. Laboratory values obtained prior to Cycle 1 Day 1 for the Treatment Phase should be repeated if the blood sample was collected more than 72 hours prior to the anticipated start of study treatment. Test results should satisfy eligibility criteria for treatment to commence.

Subjects assigned to I+VEN will receive treatment as outlined in Section 6.1. Treatment begins with 3 cycles of ibrutinib monotherapy. Investigators must request approval from medical monitor to start the venetoclax dose ramp-up phase in Cycle 4 after TLS risk assessment is completed and the appropriate TLS prophylaxis is started (see Table 8). I+VEN combination therapy will be given for 12 cycles.

Subjects assigned to G-Clb will receive obinutuzumab infusions as outlined in Section 6.2. G-Clb will be given for 6 cycles.

Subjects will report to the study site on Day 1 of each cycle for study-related procedures outlined in the Time and Events Schedules (Table 1 or Table 2). Clinical evaluations and laboratory studies may be repeated more frequently, if indicated. Treatment will be dispensed once all predose evaluations have been completed and the investigator has decided that a subject may receive treatment. Instructions for home administration and storage conditions of study treatment should be reviewed. If a subject shows signs of progression on physical examination or laboratory assessment, study treatment may continue until progression is confirmed by additional modalities. If PD is diagnosed, then the subject should discontinue study treatment, complete the End-of-Treatment Visit within 30 days (+7-day window) of the last dose of study treatment, and enter the Follow-up Phase.

End-of-Treatment

An End-of-Treatment Visit will be scheduled within 30 days (+7-day window) of the last dose of study treatment in the Treatment Phase and in the Subsequent Therapy Phase for all subjects discontinuing treatment for any reason, except for lost to follow-up, death, or withdrawal of consent for study participation. Subjects who discontinue treatment and enter the Follow-up Phase should have the End-of-Treatment Visit completed before starting any subsequent anti-leukemic treatment for CLL. If a subject is unable to return to the site for the End-of-Treatment Visit, then the subject should be contacted to collect AEs that occur within 30 days after the last dose of study treatment. Additional information on reporting of AEs is found in Section 12. Refer to the Time and Events Schedules for a complete list of procedures to be performed at the End-of-Treatment Visit.

9.1.4. Follow-up Phase

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 DEs as outlined in the Time and Events Schedule (Table 3). These subjects will also be followed for survival status.

Following disease progression, contact will be made every 24 weeks ± 7 days until study end to determine:

- Subsequent anti-leukemic therapy
- CLL treatment criteria supporting initiation of subsequent therapy
- Occurrence of new malignancy
- PRO score (EQ-5D-5L only for the first 2 post-PD visits)
- Transformation to a more aggressive histology (Richter's transformation)
- Survival status.

The EQ-5D-5L questionnaire will be administered as shown in the Time and Events Schedules. If the subject is at the site for the follow-up assessment, then the subject should complete the questionnaire. If the follow-up assessment is conducted via a telephone call with the subject, then the subject's questionnaire responses will be read over the telephone to the site staff, who will record them in the PRO instrument.

The Follow-up Phase will continue until the subject enters the Subsequent Therapy Phase (if applicable), death, lost to follow-up, consent withdrawal, or study end, whichever occurs first. A subject who progresses on therapy with single-agent ibrutinib during the Subsequent Therapy Phase may re-enter the Follow-up Phase.

It is important for survival status to be assessed and the date of death documented for each randomized subject, regardless of whether the subject received study treatment. If information on survival status and subsequent therapy is obtained via telephone contact, then written documentation of the communication must be available for review in source documents. If a subject dies, then the date and cause of death are to be reported in the appropriate eCRF.

9.1.5. Subsequent Therapy Phase

Before a subject is considered for inclusion in the Subsequent Therapy Phase, the investigator is expected to re-review the informed consent with the subject to ensure that he or she understands the purpose of, as well as the study procedures and required visits associated with, the Subsequent Therapy Phase. The eligibility criteria described in Section 9.1.5.1 will be reviewed and a clinical evaluation will be performed, including medical history review, staging (Attachment 10), and laboratory tests (including FISH analysis for del17p, del11q, del13q, and trisomy 12 for sponsor review; see Table 4). Imaging is required prior to treatment in the Subsequent Therapy Phase for subjects initially treated with I+VEN (Treatment Arm A). Results of CT scans (or magnetic resonance imaging [MRI; Section 9.2.1.1]) obtained within 60 days before start of single-agent ibrutinib treatment can be used, if the Imaging Acquisition Guidelines standards are met. Approval from the medical monitor is required for treatment with single-agent ibrutinib and treatment should be started within 72 hours of approval.

The Subsequent Therapy Phase will begin at Cycle 1 Day 1 of treatment with single-agent ibrutinib and will continue until disease progression, unacceptable toxicity, or other reasons as described in Section 10.2. The results of laboratory testing obtained of Cycle 1 Day 1 of single-agent ibrutinib treatment will be defined as the baseline values for safety assessments and treatment decisions in the Subsequent Therapy Phase. Laboratory values obtained prior to Cycle 1 Day 1 of single-agent ibrutinib should be repeated if the blood sample was collected more than 72 hours prior to the anticipated start of study treatment. Test results should satisfy eligibility criteria for treatment to commence.

Subjects will receive treatment as outlined in Section 6.3. Subjects who tolerated a reduced dose of ibrutinib during the Treatment Phase may initiate ibrutinib as a single agent at the same lower dose, per investigator's discretion. Escalation to the full dose should be considered if appropriate.

Subjects will report to the study site as outlined in Table 4 and Figure 2. Clinical evaluations and laboratory studies may be repeated more frequently, if indicated. Treatment will be dispensed once all predose evaluations have been completed and the investigator has decided that a subject may receive treatment. Instructions for home administration and storage conditions of study treatment should be reviewed. If a subject shows signs of progression on physical examination or laboratory assessment, study treatment may continue until progression is confirmed by additional modalities. If PD is diagnosed, then the subject should discontinue study treatment, complete the

End-of-Treatment Visit within 30 days (+7-day window) of the last dose of study treatment (see Section 9.1.3), and enter the Follow-up Phase.

9.1.5.1. Eligibility for the Subsequent Therapy Phase

Eligibility for the Subsequent Therapy Phase must be approved by the medical monitor following an assessment of the eligibility parameters described below and a review of relevant inclusion/exclusion criteria for overall study entry in Section 4.1 and Section 4.2.

Participation in the Subsequent Therapy Phase is not mandatory and is based on investigator's discretion.

Inclusion Criteria for Subsequent Therapy with Single-agent Ibrutinib

Study subjects must satisfy all of the following criteria to be eligible to receive single-agent ibrutinib and enter the Subsequent Therapy Phase.

1. Criterion modified per Amendment 4

   1.1 Completed the initial fixed-duration Treatment Phase as described in the protocol. Subjects randomized to Treatment Arm B may remain eligible even if protocol-specified treatment is not completed.

2. Progressive disease confirmed by IRC
3. Exhibit active CLL/SLL requiring treatment per iwCLL criteria.

Exclusion Criteria for Subsequent Therapy with Single-agent Ibrutinib

Any potential subject who meets any of the following criteria will be excluded from participating in the Subsequent Therapy Phase:

1. Any potential subject who has received any subsequent anti-leukemic therapy after the Treatment Phase will be excluded from participating in the Subsequent Therapy Phase.

NOTE: Investigators should ensure that all criteria are met. If a subject's clinical status changes after request for approval of subsequent therapy with single-agent ibrutinib, but before the first dose of study treatment such that he or she no longer meets all eligibility criteria, the subject should be excluded from treatment.

9.2. Efficacy

Efficacy evaluations will be conducted as specified in the Time and Events Schedule (Table 3 and Table 4) and will include the following:

- Disease-related symptoms and physical examination. For disease-related symptoms, subjects will be asked about the presence or absence and severity of fatigue, night sweats, fevers, weight loss, and abdominal discomfort. All post-screening physical examinations should focus on examination of lymph nodes, the liver, and spleen.
- CBC with ALC.
- CT scan of the neck, chest, abdomen, and pelvis.

- MRD: Collection of peripheral blood for central MRD analysis by flow cytometry should be done on all subjects with a response of PR or better. Collection of bone marrow aspirate for central MRD analysis by flow cytometry and NGS should be done in all responders.
- PROs as measured by the EORTC-QLQ-C30 and EQ-5D-5L questionnaires, and the FACIT-Fatigue scale.

9.2.1. Evaluations

9.2.1.1. Radiographic Imaging Assessments

Disease response should be assessed using CT scans with IV contrast of the neck (full neck views starting from the base of the skull must be obtained), chest, abdomen, and pelvis. The size of lymph nodes, the liver, and spleen should be evaluated. All imaging should be performed according to the Imaging Acquisition Guidelines (see materials in Section 15). Subjects who cannot tolerate IV contrast may have CT scans performed with oral contrast. If disease progression is suspected from physical examination or laboratory testing, additional modalities must be performed for confirmation. The subject may continue study treatment until disease progression is confirmed. CT scans should be performed according to the Time and Events Schedule (Table 3 and Table 4) until disease progression is confirmed, regardless of whether or not the subject remains on study treatment. In the Subsequent Therapy Phase, CT imaging is expected for subjects who were initially treated with I+VEN (Treatment Arm A). For subjects who were initially treated with G-Clb (Treatment Arm B), imaging is recommended only when clinically indicated and as determined by the investigator.

Magnetic resonance imaging may be used to evaluate sites of disease that cannot be adequately imaged using CT or in exceptional cases where CT scans with IV or oral contrast are contraindicated. However, the imaging modality used must remain consistent from screening through all subsequent DEs. Brain imaging and positron emission tomography scans may be done only if clinically indicated.

9.2.1.2. Definition of Measurable and Assessable Disease

Subjects must have at least 1 measurable site of disease (target lesion) to participate in the study.[28] Measurable sites of disease are defined as lymph nodes or lymph node masses >1.5 cm in longest diameter. Measurements must be determined by CT or MRI imaging. Extranodal sites of disease are considered assessable, but not measurable.

Up to 6 measurable sites of disease, clearly measurable in 2 perpendicular dimensions, will be followed for each subject. Measurable sites of disease should represent the extent of the subject's disease. As much as possible, the selection of target lesions should be from different regions of the body. Additional lesions that are identified by radiologic imaging or physical examination but are not included in the target lesion assessment should be considered as assessable (non-target) lesions and followed throughout the study. Investigators should provide a qualitative assessment of the spleen and liver at screening and in all subsequent DE visits.

9.2.1.3. Bone Marrow Assessments

A bone marrow aspirate and biopsy must be obtained during screening or up to 90 days before randomization. For subjects undergoing a baseline bone marrow assessment during the screening period, a sample of the bone marrow aspirate and biopsy should be collected for biomarker assays and MRD testing. Archived bone marrow slides for biomarkers are acceptable for patients who are not undergoing bone marrow assessments at screening. Standard CLL testing to assess morphology, immunophenotyping, and cytogenetic profile (by FISH) should be performed to completely characterize the diagnosis of CLL. A local bone marrow biopsy examination is expected to include morphologic evaluation and immunohistochemistry testing. For subjects with SLL, a lymph node biopsy may be used for similar tests. Instructions for the collection, handling, and shipment of bone marrow samples are outlined in a Laboratory Manual.

Bone marrow aspirate and biopsy samples are collected from all subjects with response of PR or better at DE3 of the Treatment Phase. The bone marrow aspirate and biopsy should be sent to a local laboratory for standard evaluation and response assessment. An additional bone marrow aspirate sample will be sent to the central laboratory for MRD analysis (as described in Section 9.2.2). At DE6 of the Treatment Phase, a central bone marrow aspirate MRD assessment is required in all subjects with a response of PR or better. Bone marrow biopsy and aspirate for local evaluations are only required for subjects on the I+VEN treatment group who were not confirmed CR at DE3 of the Treatment Phase. For subjects with a suspected PD based on new onset cytopenia, a bone marrow aspirate and biopsy should be obtained to confirm PD locally.

During the Subsequent Therapy Phase, a bone marrow biopsy is indicated to confirm a CR. Additional bone marrow evaluations may be pursued at the investigator's discretion.

9.2.2. Minimal Residual Disease Assessments

An analytically validated 8-color flow cytometry assay will be used to assess MRD.[44] Samples will be incubated with a cocktail of fluorochrome-labeled antibodies.

One million viable events will be acquired on the FACSCanto II flow cytometer, and post-acquisition analysis will be performed to determine MRD-negativity. MRD-negativity is defined as <1 CLL cell per 10,000 leukocytes or <0.01%. Peripheral blood collection for MRD analyses will begin at 12 weeks after randomization (DE1) and will continue in both treatment arms at each DE visit until disease progression. A sample of bone marrow aspirate for MRD assessment for all responding subjects (ie, response of PR or better) must be sent to the sponsor at DE3 and DE6 (as described in Section 9.2.1.3). The first draw of the bone marrow aspirate should be sent for central MRD analysis. Additional instructions for the assessment of MRD are outlined in a separate Laboratory Manual.

9.2.3. Response Categories

Assessment of response should include an evaluation for disease-related symptoms, physical examination, radiographic imaging, and blood and bone marrow testing (whenever applicable). Response categories are defined in Table 13 and in the text immediately following. All responses must be confirmed by CT scans and must last for at least 56 days to be considered confirmed.

For the purpose of study analyses, responses during the Treatment Phase will be determined by an IRC blinded to study treatment information and independent of investigators and personnel involved in the conduct of the study. As part of the central IRC review, imaging studies will be assessed by independent radiologists and relevant clinical data will be assessed by an independent oncologist. The IRC process will be described in detail in a separate charter.

During the Subsequent Therapy Phase, responses will be based on the investigator's assessment. If needed, confirmation of responses by the IRC may be pursued by the sponsor for regulatory purposes.

Table 13: Criteria for Response Categories

Parameter	CR	PR	PD
Group A			
Lymphadenopathy[a]	None >1.5cm	Decrease ≥50%[b]	increase ≥50% or appearance of new lesions >1.5 cm
Hepatomegaly	None	Decrease ≥50%	increase ≥50% or appearance of new hepatomegaly
Splenomegaly	None	Decrease ≥50%	increase ≥50% or appearance of new splenomegaly
Blood lymphocytes	<4000/μL	Decrease ≥50% from baseline	increase ≥50% over baseline[d]
Marrow[c]	Normocellular, <30% lymphocytes, no B lymphoid nodules. Hypocellular marrow defines CRi	50% reduction in marrow infiltrates or B lymphoid nodules	
Group B			
Platelet count	>100,000/μL	>100,000/μL or increase ≥50% over baseline	Decrease of ≥50% from baseline secondary to CLL
Hemoglobin	>11 g/dL	>11g/dL or increase ≥50% over baseline	Decrease of >2g/dL from baseline secondary to CLL
Neutrophils[c]	>1500/μL	>1500/μL or increase ≥50% over baseline	

Abbreviations: CLL=chronic lymphocytic leukemia; CR=complete response; CRi=complete response with an incomplete marrow recovery; PD=disease progression; PR=partial response

[a] Sum of the products of multiple lymph nodes (as evaluated by CT scans)
[b] Defined as a decrease in lymph nodes of ≥50% either in the sum products of the diameter of up to 6 lymph nodes, or in the largest diameter of the enlarged lymph node detected prior to the therapy, as well as no increase in any lymph node and no new enlarged lymph nodes. Note: in small lymph nodes <2 cm, an increase of <25% is not considered to be significant.
[c] This parameter is not relevant for the PD category.
[d] Subjects with treatment-related lymphocytosis should remain on study treatment in the absence of other evidence of progressive disease.
Note: Group A defines the tumor load and Group B defines the function of the hematopoietic system
CR: all of the criteria need to be met and subjects have to lack disease-related symptoms.
PR: At least 2 criteria from Group A plus 1 of the criteria from Group B must be met.
NOTE: If only 1 measurable Group A criterion is present at baseline (eg, enlarged lymph nodes but no other abnormality), per recent clarifications of the iwCLL criteria[27,28] these subjects are still considered evaluable for PR if the given parameter improves by at least 50% for a minimum of 56 days. Subjects are also required to have 1 Group B parameter, which can either be improvement in a previously abnormal finding or the persistence of a normal value for at least 56 days as a result of therapy.
PD: at least 1 of the above criteria from Group A or B are met; or transformation to more aggressive histology (eg, Richter's transformation); or a ≥50% increase from the nadir count confirmed on ≥2 serial assessments if the ALC is ≥30,000/μL and lymphocyte doubling time is rapid, unless considered treatment-related lymphocytosis. A new organ infiltrate, bone lesion, ascites, or pleural effusion confirmed due to CLL would also be considered PD.
Reference: modified from 2008 iwCLL criteria[26,27,28]

Complete Response with an Incomplete Marrow Recovery (CRi):

CRi is defined as a complete response with peripheral cytopenia and incomplete recovery of the bone marrow, manifested by persistent cytopenias. Subjects who have a CRi fulfill the criteria for a CR, but continue to have persistent anemia, thrombocytopenia, and/or neutropenia, with a hypocellular bone marrow confirmed by bone marrow biopsy. These cytopenias are considered due to drug toxicity in the bone marrow and are not related to CLL.

Nodular Partial Response (nPR):

nPR is a response that meets the criteria for CR, but the bone marrow biopsy shows lymphoid nodules, reflecting residual disease.

Partial Response with Lymphocytosis (PRL):

PRL is a response where subjects meet the criteria for a PR and have persistent lymphocytosis.

Stable Disease:

Subjects who do not meet the criteria for CR, CRi, nPR, PR, PRL, or PD.

Treatment-related Lymphocytosis:

Treatment-related lymphocytosis is defined as an elevation in blood lymphocyte count of ≥50% compared with baseline that occurs in the setting of unequivocal improvement in at least 1 other disease-related parameter, including lymph node size, spleen size, blood counts (hemoglobin and platelet count), or disease-related symptoms. Treatment-related lymphocytosis is isolated lymphocytosis that occurs when no other criteria for PD are met. It will not be considered PD.

9.2.4. Patient-reported Outcomes

PRO assessments will be conducted as described in the Time and Events Schedules. Collection of PRO assessments will stop after the primary PFS analysis is completed.

Three PRO instruments will be administered in this study: 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). The EORTC QLQ-C30 is a 30-item general cancer assessment that incorporates 5 functional scales (physical, role, emotional, cognitive, and social functioning), 3 symptom scales (fatigue, nausea/vomiting, and pain), a global health status and QoL scale (2 items), and 6 single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). Scores range from 0 to 100 (for functional and global QoL scales, higher scores indicate a better level of functioning). Differences of ≥10 points on EORTC scales are considered clinically important.

The FACIT-Fatigue scale is a 13-item instrument designed to assess aspects of fatigue/tiredness in patients with cancer or other chronic diseases, including the impact on daily activities and functioning. Items are scored on a 0–4 response scale (0=not at all; 4=very much). All items are summed to create a single fatigue score ranging from 0 to 52, with higher scores indicating better functioning or less fatigue. A difference of ≥3 points in FACIT-Fatigue score is considered clinically important.

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.

9.3. Pharmacokinetics

Plasma samples from venous blood collections for all subjects in Treatment Arm A will be used to evaluate the pharmacokinetics of ibrutinib and its metabolite PCI-45227, and venetoclax. Plasma collected for pharmacokinetic analyses may additionally be used to evaluate safety and efficacy questions, drug characteristics, or certain biomarkers for future research. Genetic analyses will not be performed on these samples. Subject confidentiality will be maintained.

9.3.1. Pharmacokinetic Evaluations

Venous blood samples will be collected at steady-state from all subjects assigned to I+VEN treatment for measurement of trough plasma concentrations of ibrutinib, PCI-45227, and venetoclax at time points specified in the Time and Events Schedule for the Treatment Phase for Treatment Arm A (Table 1). These samples will be tested by the sponsor or sponsor's designee.

The exact dates and times of blood sampling must be recorded, together with the drug intake time on the day before sampling. Refer to the Laboratory Manual for sample collection requirements. Collected samples must be stored under the specified and controlled conditions for the temperatures indicated in the Laboratory Manual. Additional information about the collection, handling, and shipment of biological samples can be found in the Laboratory Manual.

9.3.2. Pharmacokinetic Analytical Procedures

Pharmacokinetics

Plasma samples will be analyzed to determine concentrations of ibrutinib, PCI-45227, or venetoclax. Analysis will be performed using validated, specific, and sensitive liquid chromatography/mass spectrometry/mass spectrometry methods by or under the supervision of the sponsor.

9.3.3. Pharmacokinetic Parameters

The PK parameter is defined as:

$C_{trough,ss}$=Concentration at end of dosing interval (24h) at steady-state

The ibrutinib, PCI-45227, and venetoclax $C_{trough,ss}$ data will be summarized by descriptive statistical methods.

9.4. Biomarkers

To better understand the mechanism of action of ibrutinib and to develop predictors of resistance, bone marrow, peripheral blood, and buccal swab samples will be collected as specified in the Time and Events Schedules.

Plasma samples may be analyzed to identify biomarkers that may be related to treatment-induced changes and that may be indicative of response to and relapse following I+VEN treatment. Blood samples collected at screening will be analyzed for *IGHV* mutational status, a stratification factor for randomization. Additional blood samples collected may be evaluated for protein expression and other RNA/DNA signatures that may predict primary or acquired resistance. Bone marrow aspirate may be characterized by gene expression profiling and somatic mutation analysis by NGS to evaluate for potential biomarkers that may contribute to sensitivity or resistance to therapy in CLL. Samples may be evaluated by other similar technologies to evaluate protein or RNA expression, cytogenetics or for somatic DNA analysis.

Plasma and bone marrow samples will be evaluated for MRD by flow cytometry. MRD analysis by NGS-based methods may subsequently be performed.

Stopping Analysis

Biomarker analyses are dependent upon the availability of appropriate biomarker assays and clinical response rates. Biomarker analysis may be deferred or not performed, if during or at the end of the study, it becomes clear that the analysis will not have sufficient scientific value for biomarker evaluation, or if there are not enough samples or responders to allow for adequate biomarker evaluation. In the event the study is terminated early or shows poor clinical efficacy, completion of biomarker assessments is based on justification and intended utility of the data.

9.5. Safety Evaluations

The study will include the following evaluations of safety and tolerability according to the time points provided in the Time and Events Schedules. Any clinically significant abnormalities persisting at the end-of-treatment must be followed by the investigator until resolution, until a clinically stable endpoint is reached, or until the end of the study.

Adverse Events

Adverse events will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legal representative) for the duration of the study. Adverse events will be followed by the investigator as specified in Section 12. Non-hematologic AEs and hematologic AEs events will be graded according to specifications listed in Section 12.1.3.

Clinical Laboratory Tests

Complete blood counts obtained per the Time and Events Schedules should be performed at the laboratory associated with the treating institution, except where noted below. Laboratory certificates or accreditation and normal ranges of the laboratory facility at the site must be submitted to the sponsor before the enrollment of any subject at the site. If the subject will have laboratory assessments conducted at a facility other than the one associated with the investigational site, then the investigator must submit to the sponsor laboratory certificates or accreditation and normal ranges for that facility as well.

Blood samples to assess the safety of study treatment will be collected as specified in the Time and Events Schedules. The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. For example, laboratory abnormalities leading to an action regarding study treatment (dose change, dose interruption, cycle delay, or treatment discontinuation) or the start of concomitant therapy should be reported. For each laboratory abnormality reported as an AE, the following laboratory values should be reported in the laboratory section of the eCRF: the value indicative of the onset of each toxicity grade, the most abnormal value observed during the AE, and the value supporting recovery to Grade ≤1 or to baseline values.

The following clinical laboratory tests must be performed by the laboratory facility associated with the study site, as specified in the Time and Events Schedules:

- Hematology Panel
  -hemoglobin
  -white blood cell count
  -platelet count
  -ANC
  -ALC

- Serum Chemistry Panel
  -sodium
  -potassium
  -creatinine
  -ALT
  -AST
  -alkaline phosphatase
  -albumin
  -total bilirubin
  -uric acid
  -calcium
  -phosphate
  -lactic acid dehydrogenase

For the convenience of subjects assigned to G-Clb treatment group, predose blood counts and serum chemistry testing on Day 15, Cycles 2 to 6, may be done outside the treating institution. Similarly, for subjects treated with I+VEN (Treatment Arm A in the Treatment Phase) or single-agent ibrutinib (in the Subsequent Therapy Phase), during cycles which do not require clinic attendance (see the Time and Events Schedule [Table 1, Table 4, Figure 1, and Figure 2]) serum chemistry and hematology monitoring may be done outside of the treating institution. However, in both circumstances, the treating physician must ensure that he/she has access to and is able to perform timely review of laboratory results from the outside facility. Furthermore, the treating physician must have a clear line of communication with subjects to ensure that treatment decisions made after review of outside laboratory reports are communicated directly to the subject. Only clinically relevant laboratory abnormalities (ie, those corresponding to an AE or a dose change) should be reported in the eCRF.

- Coagulation
  -aPTT
  -INR

- Hepatitis B Screening
  -Hepatitis B surface antigen
  -Hepatitis B core antibody

Hepatitis B virus DNA PCR needs to be performed if Hepatitis B core antibody is positive. Hepatitis B virus DNA PCR must be negative in subjects who are Hepatitis B core antibody positive to be eligible for the study. During study treatment and for at least 12 months following the last dose of study treatment, regular monitoring of Hepatitis B DNA PCR and liver enzymes, and prophylactic antiviral medication, should be considered per published guidelines for subjects with a history of Hepatitis B infection.[40]

- Hepatitis C Screening
  -Hepatitis C antibody

Subjects who test positive for Hepatitis C antibody are eligible if previously treated and with a sustained viral response, defined as a negative viral load by Hepatitis C virus RNA PCR testing.

- Urine or serum β-hCG pregnancy testing for women of childbearing potential only
- Beta2-microglobulin
- Additional laboratory tests (eg, absolute reticulocyte counts, Coombs tests, blood urea nitrogen, glucose, creatine phosphokinase, haptoglobin) obtained because of an AE must be documented at an unscheduled visit.

Electrocardiogram

An electrocardiogram (ECG) will be performed for all subjects at study entry and during screening for subsequent therapy with ibrutinib. Testing should be obtained in a quiet setting without distractions (eg, television, cell phones). Abnormalities noted at baseline and during screening for subsequent therapy with ibrutinib should be included in the medical history. ECGs may be repeated at any time during the study if clinically indicated, particularly for subjects with symptoms related to cardiac arrhythmias. For optimal monitoring and management of cardiovascular toxicities while on the study, consider consultation with a cardiologist.

Vital Signs

Temperature, pulse/heart rate, and blood pressure will be recorded at screening. Assessment of pulse/heart rate and blood pressure is expected at every protocol-specified visit. Blood pressure and pulse/heart rate measurements should be preceded by at least 5 minutes of rest in a quiet setting without distractions (eg, television, cell phones). Clinically significant abnormalities should be recorded as AEs. If an abnormal heart rhythm is suspected, further investigation (ECG and/or Holter monitor) is required per investigator's discretion.

Physical Examination

A complete physical examination must be conducted at screening, in all DE visits (Treatment Phase, Subsequent Therapy Phase), and before the initiation of treatment with single-agent ibrutinib (Subsequent Therapy Phase). The status of nodal lesions, the liver, and spleen must be reported at each DE visit. Clinically significant abnormalities should be recorded as AEs. Weight will be measured as specified in the Time and Events Schedules.

9.6. Benefit-risk Evaluations

Benefit-risk assessment of I+VEN compared with G-Clb will be conducted by comparing between-treatment differences of key efficacy and safety endpoints. Efficacy endpoints may include PFS, MRD-negative disease status, OS, time-to-next treatment, and improvement in PRO measures. Safety endpoints may include major hemorrhage, minor hemorrhage, leukostasis, serious infections, interstitial lung disease, atrial fibrillation, TLS, non-melanoma skin cancer, diarrhea, rash, hypertension, infusion reactions and other serious adverse events (SAEs). Safety endpoints that show no between-treatment differences will be noted but may be excluded from the benefit-risk analyses. Adverse events not in this list, but that show a clinically meaningful between-treatment difference may be included.

9.7. Sample Collection and Handling

The actual dates and times of sample collection must be recorded in a laboratory requisition form. Refer to the Time and Events Schedules for the timing and frequency of all sample collections. Instructions for the collection, handling, and shipment of samples are outlined in a separate Laboratory Manual.

10. SUBJECT COMPLETION/ WITHDRAWAL

10.1. Completion

A subject will be considered to have completed the study if he or she dies before the end of the study, or has not been lost to follow-up or withdrawn consent before the end of study (see end of study definition in Section 17.9.1, Study Completion/End of Study).

10.2. Discontinuation of Study Treatment

Discontinuation of study treatment does not result in automatic withdrawal of the subject from the study. Subjects who discontinue study treatment should continue to have assessments performed as specified in the Time and Events Schedules or DEs prior to progression). A subject's study treatment must be discontinued if any of the following occurs:

- The subject experiences disease progression or relapse
- The subject experiences unacceptable toxicity
- The subject becomes pregnant
- The subject refuses further treatment with the study treatment
- The investigator believes that for safety reasons (eg, AE) it is in the best interest of the subject to stop treatment.

The investigator must notify the sponsor within 24 hours if a subject has been diagnosed with disease progression and provide documentation of the diagnosis for review by the medical monitor. If a subject shows signs of disease progression on physical examination or laboratory assessment, the subject may continue study treatment until disease progression is confirmed by other modalities (ie, CT scan, bone marrow biopsy).

10.3. Withdrawal From the Study

A subject will be automatically withdrawn from the study for any of the following reasons:

- Lost to follow-up;
- Withdrawal of consent;
- Sponsor discontinues study.

If a subject is lost to follow-up, then every reasonable effort must be made by the study site personnel to contact the subject and determine the reason for discontinuation of treatment, withdrawal of consent, and/or failure to follow-up. All measures taken to establish contact with the subject must be documented.

When a subject withdraws before completing the study, the reason for withdrawal must be documented in the eCRF and in the source document. Study treatment assigned to the withdrawn subject may not be assigned to another subject. Subjects who withdraw will not be replaced. If a subject withdraws from the study before completing the assigned treatment, end-of-treatment assessments should be obtained. If the reason for withdrawal from the study is withdrawal of consent, then no additional assessments are allowed.

10.4. Withdrawal From the Use of Research Samples

The subject may withdraw consent for use of samples collected for research (refer to Section 16.2.5, Long-Term Retention of Samples for Additional Future Research). In such a case, samples collected from the subject will be destroyed. Details of sample retention for research are presented in the main ICF.

11. STATISTICAL METHODS

Statistical analysis will be done by the sponsor or under the authority of the sponsor. A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below. Specific details will be provided in the Statistical Analysis Plan (SAP).

11.1. Analysis Sets

The ITT population is defined as all subjects randomized into the study and will be classified according to assigned treatment group, regardless of the actual treatment received. This population will be used for efficacy analyses including, but not limited to PFS, MRD-negativity, and OS, and all analyses of disposition, demographic, and baseline disease characteristics.

The safety population is defined as all randomized subjects who receive at least 1 dose of study treatment. This population will be used for all safety analyses and all analyses of treatment compliance and exposure. All data will be analyzed according to the treatment that subjects actually received.

The pharmacokinetic-evaluable population is defined as all randomized subjects who received at least 1 dose of ibrutinib and had at least 1 post-treatment pharmacokinetic sample.

The biomarker population will include all randomized subjects with sufficient malignant cells collected from at least 1 timepoint during the study.

11.2. Sample Size Determination

This study is designed to evaluate the effect of treatment on PFS and is powered for this primary endpoint. A median PFS of 27 months is reported for the G-Clb when it is used to treat patients with treatment-naïve CLL.[21] 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 I+VEN and 100 subjects into the G-Clb treatment groups) to observe 71 PFS events. No interim analysis is planned due to the small sample size and short accrual period of this study,

plus the timing of interim analysis may not allow for PFS data to be mature for analysis. The study is designed to detect a HR of 0.5 for the I+VEN treatment group relative to the G-Clb group (corresponding to an improvement of 100% in median PFS, eg, 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.

11.3. Subject Information

The distribution of subjects by treatment group for each of the analysis populations will be provided. The number of subjects enrolled, dosed, and discontinued will be summarized. Treatment discontinuation will be summarized according to the reasons for discontinuation and by treatment group.

Demographic and baseline vital sign variables will include age, sex, race, ethnicity, weight, and blood pressure. Baseline disease characteristics (documented in the source documents and eCRF) will include time from initial diagnosis to randomization, histological diagnosis (CLL, SLL), stage of disease, and ECOG PS grade (0, 1, 2).

11.4. Efficacy Analyses

Descriptive statistics will be used to summarize the data. For continuous variables, number of observations, means, standard deviations, medians, and ranges will be used. For discrete variables, frequency will be summarized. For time-to-event variables, Kaplan-Meier estimates will be provided.

The comparisons between the 2 treatment groups will be performed as follows: for the continuous variable representing change from baseline to a postbaseline timepoint, analysis of variance will be used. For discrete variables, Cochran-Mantel-Haenszel chi-square test will be used. For time-to-event variables, log-rank test will be used. All tests will be conducted at a 2-sided alpha level of 0.05, and 95% confidence intervals (CIs) will be provided, unless stated otherwise.

11.4.1. Primary Endpoint

The primary endpoint of PFS is defined as duration from the date of randomization to the date of disease progression or death, whichever occurs first. The primary efficacy analysis will be based on the IRC assessment of PD in the ITT population. The Kaplan-Meier method will be used to estimate the distribution of PFS for each treatment group. The stratified log-rank test will be used to compare PFS between the 2 treatment groups, with stratification factors *IGHV* mutational status (mutated vs. unmutated vs. not available) and presence of del11q (yes vs. no). The median PFS will be provided for each treatment group and the HR for I+VEN relative to G-Clb and its associated 95% CI will be calculated based on the Cox proportional hazards model stratified by the stratification factor.

The sensitivity analyses for PFS based on investigator assessment and using different censoring mechanisms will be performed similarly. Other exploratory analyses, such as sensitivity analysis to address the potential effect of an unequal number of subject visits that could result in unscheduled tumor assessments because of the different treatment schedules in the 2 groups, will be performed as appropriate.

11.4.2. Secondary Endpoints

The secondary endpoints are defined as follows:

- MRD-negative rate is defined as the proportion of subjects who are MRD-negative in the bone marrow (ie, <1 CLL cell per 10,000 leukocytes or <0.01%). All randomized subjects will be included in this analysis.
- CR rate is defined as the proportion of subjects who achieve CR.
- ORR is defined as the proportion of subjects who achieve a response (CR, CRi, nPR, and PR).
- Duration of response is defined as duration in days from the date of initial documentation of a response to the date of first documented evidence of PD or death.
- OS is measured from the date of randomization to the date of the subject's 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.
- Time-to-next treatment is measured from the date of randomization to the start date of any anti-leukemic treatment subsequent to the study treatment. Subjects without subsequent treatment will be censored at the date of the last site visit.
- Sustained hemoglobin improvement rate, defined as the proportion of subjects who achieve an increase of hemoglobin levels from baseline by ≥2 g/dL and lasts for at least 56 days without blood transfusion or growth factors.
- Sustained platelet improvement rate, defined the proportion of subjects who achieve an increase of platelet levels from baseline by ≥50% and lasts for at least 56 days without blood transfusion or growth factors.

For time-to-event endpoints, the Kaplan-Meier method will be used to estimate the distribution of OS (including the 24-month survival rate), duration of response and time-to-next treatment for each treatment group. Median times to event with 2-sided 95% CIs will be estimated. The log-rank test accounting for stratification factor will be used for treatment comparison except for duration of response. A Cox proportional hazards model will be used to provide estimates of HRs with 95% CIs.

For categorical endpoints, the Cochran-Mantel-Haenszel chi-square test with stratification factor will be used to compare the ORR, CR rate, the MRD-negativity remission rate and rates of hemoglobin and platelet improvement between the treatment groups.

Hierarchical gatekeeping testing procedure will be implemented for key secondary efficacy endpoints of OS, ORR, CR rate, MRD-negative rate, time-to-next anti-leukemic treatment, and time to worsening of PRO scores (Section 11.4.3) to maintain the overall control of study-wise Type I error. The sequential testing order of secondary efficacy endpoints and time to worsening for PRO endpoints will be determined later and specified in the SAP.

11.4.3. PRO Endpoints

PRO measures listed in Section 9.2.4 will be analyzed using the methods specified in Section 11.4. For individual items and sub-scale scores within the PRO measures, descriptive statistics (mean, standard deviation, median, and range) will be calculated for each time point, for changes from baseline at each time point, as well as for changes from baseline to the last value. Mixed-model repeated measures will be used for longitudinal analysis of PRO score change for EORTC QLQ-C30 global health and physical function, FACIT-Fatigue total score, and EQ-5D-5L utility score and VAS score.

Time to worsening in the PRO scores from the EORTC QLQ-C30 (global health status and physical functioning scores) and FACIT-Fatigue (total score) and EQ-5D-5L utility score and VAS score is measured from the date of randomization to the start date of worsening. Worsening is defined by clinically important negative change (Section 9.2.4). Time to worsening in PRO scores will be compared using the similar approach for time-to-event secondary endpoints (Section 11.4.2).

11.4.4. Subsequent Therapy Evaluations

A pooled analysis of outcome after ibrutinib re-treatment may be pursued using data from the current study and another clinical trial (ie, Study PCYC-1142-CA). Details of the statistical analysis will be described in a separate SAP, as applicable.

11.5. Pharmacokinetic Analyses

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.

11.6. Biomarker Analyses

Biomarker studies are designed to identify molecular and protein markers associated with response to and relapse following therapy. Analyses will be performed within each treatment group in total and stratified by clinical covariates or molecular subgroups. The associations of biomarkers with clinical response or time-to-event endpoints will be assessed using the appropriate statistical methods (analysis of variance, categorical, or survival model), depending on the endpoint. Results may be presented in a separate report.

11.7. Safety Analyses

The safety analysis population will consist of all randomized subjects who receive at least 1 dose of study treatment. The number and percent of subjects with TEAEs will be summarized according to intensity using the NCI-CTCAE Version 4.03, drug relationship, and outcome. Laboratory data will be summarized and descriptive statistics will be calculated. Changes in physical examination parameters will be summarized.

The safety variables to be analyzed include AEs, clinical laboratory tests (hematology and chemistry), physical examination results, and deaths. Reduction in TLS risk will be assessed following ibrutinib monotherapy in Treatment Arm A (I+VEN). Safety variables are to be tabulated by descriptive statistics (n, mean, median, standard deviation, minimum, and maximum; or n and percent). No formal statistical testing is planned.

Adverse Events

The verbatim terms used in the eCRF by investigators to identify AEs will be coded using the Medical Dictionary for Regulatory Activities. All reported AEs with onset during the treatment phases (ie, TEAEs, and AEs that have worsened since baseline) will be included in the analysis. For each AE, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized by treatment group.

Treatment-emergent AEs are AEs that occur after the first dose of study treatment, and within 30 days following the last dose of study treatment; any AE that is considered study treatment-related regardless of the start date of the event; or any AE that is present at baseline but worsens in severity or is subsequently considered treatment-related by the investigator. Adverse events of special interest with ibrutinib are the events of major hemorrhage. Subjects with AEs of special interest may be counted or listed. Adverse events of special interest will be summarized similarly to TEAEs.

Clinical Laboratory Tests

Laboratory tests will be summarized by hematology and serum chemistry, separately. Selected hematologic and chemistry laboratory parameters are detailed in Section 9.5. Descriptive statistics will be provided for the values of selected clinical laboratory tests at each scheduled on-treatment evaluation including the final value by treatment group. Percent change from baseline to each scheduled on-treatment evaluation and to the final value will also be summarized. For selected variables, the mean value and mean percent change over time will be presented graphically.

A summary of the shifts in selected laboratory hematology and serum chemistry parameters from baseline to the worst toxicity grade during the study will be provided. The worst toxicity grade during the study will be tabulated.

Physical Examination

Descriptive statistics of changes from baseline will be summarized at each scheduled time point.

Physical examination findings will be summarized at each scheduled time point. Descriptive statistics will be calculated at baseline and for observed values and changes from baseline at each scheduled time point. Frequency tabulations of the abnormalities will be made.

11.8. Benefit-Risk Analyses

For benefit-risk analyses, between-treatment differences will be shown with absolute rate or other difference measures and corresponding 95% CIs. Both continuous and dichotomized versions of continuous endpoints will be shown. Adverse events may be further characterized by their NCI-CTCAE grade. Results will be displayed in tabular and forest plot form. Additional details will be provided in the SAP.

11.9. Data Monitoring Committee

An independent DMC will be 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 at least one medical expert in the relevant therapeutic area and at least 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.

12. ADVERSE EVENT REPORTING

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established Standard Operating Procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

12.1. Definitions

12.1.1. Adverse Event Definitions and Classifications

Adverse Event

An AE is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An AE does not necessarily have a causal relationship with the intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per International Conference on Harmonisation [ICH])

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Note: The sponsor collects AEs starting with the signing of the ICF (refer to Section 12.3.1, All Adverse Events, for time of last AE recording).

Serious Adverse Event

An SAE based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
  (The subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is Medically Important.*

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life-threatening, or result in death or hospitalization, but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An AE is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For ibrutinib, the expectedness of an AE will be determined by whether or not it is listed in the IB. For venetoclax, chlorambucil or obinutuzumab, the expectedness of an AE will be determined by whether or not it is listed in the approved labels.[22,39,54]

Adverse Event Associated With the Use of the Intervention

An AE is considered associated with the use of the treatment if the attribution is possible, probable, or very likely by the definitions listed in Section 12.1.2.

12.1.2. Attribution Definitions

Not Related

An AE that is not related to the use of the intervention.

Doubtful

An AE for which an alternative explanation is more likely, eg, concomitant drug(s), concomitant disease(s), or the relationship in time suggests that a causal relationship is unlikely.

Possible

An AE that might be due to the use of the intervention. An alternative explanation, eg, concomitant drug(s), concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.

Probable

An AE that might be due to the use of the intervention. The relationship in time is suggestive (eg, confirmed by dechallenge). An alternative explanation is less likely, eg, concomitant drug(s), concomitant disease(s).

Very Likely

An AE that is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, eg, concomitant drug(s), concomitant disease(s). The relationship in time is very suggestive (eg, it is confirmed by dechallenge and rechallenge).

12.1.3. Severity Criteria

Adverse event severity is a clinical determination of the intensity of an AE. The severity assessment for any non-hematologic AE or SAE should be completed using the NCI-CTCAE, Version 4.03 (see below for hematologic AEs and SAEs). Any AE or SAE not listed in the NCI-CTCAE Version 4.03 will be graded according to the investigator clinical judgment by using the standard grades as follows:

Grade 1 Mild: Awareness of symptoms that are easily tolerated, causing minimal discomfort, and not interfering with everyday activities

Grade 2 Moderate: Sufficient discomfort is present to cause interference with normal activity

Grade 3 Severe: Extreme distress, causing significant impairment of functioning or incapacitation. Prevents normal everyday activities

Grade 4: Life-threatening or disabling AE

Grade 5: Death related to the AE

The investigator should use clinical judgment in assessing the severity of events not directly experienced by the subject (eg, laboratory abnormalities).

Hematological Adverse Events

Evaluation of hematologic toxicity in subjects with advanced CLL must consider the high frequency of bone marrow involvement at the initiation of therapy. The standard hematologic grading system for solid tumors may not always apply since a substantial proportion of subjects will be considered to have Grade 2 to 4 hematologic toxicity before any therapy is given.

Therefore, the scheme in Table 14 must be used to assess the severity of hematologic deterioration in the study, in accordance with the iwCLL recommendations.[28]

Table 14: iwCLL Grading Scale for Hematologic Toxicity in CLL Studies

Decrease in Platelets or Hgb (nadir) from Pre-treatment Value, %	ANC/µL (nadir)[c]	Toxicity Grade
0-10%[a]	≥2000	0
11%-24%[a,b]	≥1500 and <2000	1
25%-49%[a,b]	≥1000 and <1500	2
50%-74%[a,b]	≥500 and <1000	3
≥75%[a,b]	<500	4

[a] Platelet counts must be below normal levels for Grades 1 to 4: If, at any level of decrease, the platelet count is <20 x 10^9/L (20,000/µL), this will be considered Grade 4 toxicity, unless a severe or life-threatening decrease in the initial platelet count (eg, <20 x 10^9/L [20,000/µL]) was present pre-treatment, in which case the subject is not evaluable for toxicity referable to platelet counts.

[b] Hemoglobin levels must be below normal levels for Grades 1 to 4. Baseline and subsequent hemoglobin determinations must be performed before any given transfusions.

[c] If the ANC reaches <1 x 10^9/L (1,000/µL), it should be a Grade 3 toxicity. If the ANC was <1 x 10^9/L (1,000/µL) before therapy, the subject is not evaluable for toxicity referable to the ANC.

Reference: Hallek 2008[28]

12.2. Special Reporting Situations

Safety events of interest on a sponsor study intervention that may require expedited reporting or safety evaluation include, but are not limited to:

- Overdose of a sponsor study intervention
- Suspected abuse/misuse of a sponsor study intervention
- Accidental or occupational exposure to a sponsor medicinal product
- Medication error involving a sponsor product (with or without subject exposure to the sponsor medicinal product, eg, name confusion).

Special reporting situations should be recorded in the eCRF. Any special reporting situation that meets the criteria of an SAE should be recorded on the SAE page of the eCRF.

12.3. Procedures

12.3.1. All Adverse Events

All subjects who receive treatment will be considered evaluable for toxicity. All AEs and special reporting situations, whether serious or nonserious, will be reported from the time a signed and dated ICF is obtained until 30 days following the last dose of study treatment, or until the start of a subsequent systemic anti-leukemic therapy, if earlier. For subjects participating in the Subsequent Therapy Phase, all AEs shall be reported from the date of the first dose until 30 days after the last dose of ibrutinib, or until the start of a second subsequent therapy, if earlier. Adverse events reported after 30 days following the last dose of study treatment should also be reported if considered related to study treatment. Resolution information after 30 days should be provided. All Grade 3 or Grade 4 AEs considered related to study treatment must be followed until recovery to baseline or Grade ≤1 or until no further improvement is expected. Cardiac AEs

of Grade 2 or higher will be followed until improvement to baseline or Grade ≤1 or no further improvement is expected. Any unresolved events will be followed for a maximum of 6 months. All AEs of special interest as defined in Section 12.3.3 related to bleeding or resulting in bleeding complications must be followed until recovery or until there is no further improvement.

Expected progression of disease should not be considered an AE (or SAE). However, if determined by the investigator to be more likely related to the study treatment than the underlying disease, the clinical signs or symptoms of progression and the possibility that the study treatment is enhancing disease progression, should be reported per the usual reporting requirements (see Section 12.1).

Asymptomatic treatment-related lymphocytosis should also not be considered an AE. Subjects with treatment-related lymphocytosis should remain on study treatment and continue with all study-related procedures.

Serious AEs, including those spontaneously reported to the investigator within 30 days after the last dose of study treatment, must be reported using the Serious Adverse Event Form. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol. Otherwise, all events that meet the definition of an SAE will be reported as SAEs, regardless of whether they are protocol-specific assessments.

All AEs, regardless of seriousness, severity, or presumed relationship to study treatment, must be recorded using medical terminology in the source document and the eCRF. All records will need to capture the details of the duration and the severity of each episode, the action taken with respect to the study treatment, investigator's evaluation of its relationship to the study treatment, and the subject outcome. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the eCRF their opinion concerning the relationship of the AE to study treatment. All measures required for AE management must be recorded in the source document and reported according to sponsor instructions. The intensity (severity) of non-hematological AEs will be assessed using NCI-CTCAE Version 4.03. Hematological AEs will be assessed using the iwCLL criteria.

The sponsor assumes responsibility for appropriate reporting of AEs to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all SAEs that are unlisted (unexpected) and associated with the use of the treatment. The investigator (or sponsor where required) must report these events to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB.

Subjects (or their designees, if appropriate) must be provided with a "study card" and instructed to carry this card with them for the duration of the study indicating the following:

- Study number
- Statement, in the local language(s), that the subject is participating in a clinical study

- Investigator's name and 24-hour contact telephone number
- Local sponsor's name and 24-hour contact telephone number (for medical staff only)
- Site number
- Subject number

12.3.2. Serious Adverse Events

All SAEs occurring during the study must be reported to the appropriate sponsor contact person by study site personnel within 24 hours of their knowledge of the event.

Information regarding SAEs will be transmitted to the sponsor using the Serious Adverse Event Form, which must be completed and signed by a physician from the study site and transmitted to the sponsor within 24 hours. The initial and follow-up reports of an SAE should be made by facsimile (fax).

All SAEs that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study intervention or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts).

Suspected transmission of an infectious agent by a medicinal product will be reported as an SAE. Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a subject's participation in a study must be reported as an SAE, except hospitalizations for the following:

- A standard procedure for protocol therapy administration will not be reported as a SAE. Hospitalization or prolonged hospitalization for a complication of therapy administration will be reported as a SAE.
- The administration of blood or platelet transfusion. Hospitalization or prolonged hospitalization for a complication of such transfusion remains a reportable SAE.
- A procedure for protocol/disease-related investigations (eg, scans, sampling for laboratory tests, bone marrow sampling, biomarker blood sampling). Hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable SAE.
- Prolonged hospitalization for technical, practical, or social reasons in the absence of an AE.

- A procedure planned before entry into the study (must be documented in the eCRF). Prolonged hospitalization for a complication considered to be at least possibly related to the study treatment remains a reportable SAE.

12.3.3. Adverse Events of Special Interest

Specific AEs or groups of AEs will be followed as part of standard safety monitoring activities by the sponsor. These events should be reported to the sponsor within 24 hours of awareness irrespective of seriousness (ie, serious and nonserious AEs) following the procedure described above for SAEs and will require enhanced data collection.

Major Hemorrhage

Major hemorrhage is defined as:

- Any treatment-emergent hemorrhagic AE of Grade 3 or higher.*
- Any treatment-emergent SAE of bleeding of any grade.
- Any treatment-emergent CNS hemorrhage/hematoma of any grade.

**All hemorrhagic AEs requiring a transfusion of red blood cells should be reported as a Grade 3 or higher AEs per NCI-CTCAE Version 4.03.*

12.3.4. Other Malignancies

In addition to routine AE reporting, all new malignant tumors including solid tumors, skin malignancies and hematologic malignancies are to be reported for the duration of study treatment and during any protocol-specified follow-up periods, including post-progression follow-up for OS. If observed, enter data in the corresponding eCRF.

12.3.5. Eye-related Adverse Events

New or worsening eye-related symptoms that are Grade 2 or higher, or a symptom that was Grade 2 or higher at baseline and worsened during the study, should be evaluated by an ophthalmologist when appropriate.

12.3.6. Pregnancy

All initial reports of pregnancy in female subjects or partners of male subjects must be reported to the sponsor by the investigational staff within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, and congenital anomalies, ectopic pregnancy) are considered SAEs and must be reported using the Serious Adverse Event Form. Any subject who becomes pregnant during the study must discontinue further study treatment. Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

Venetoclax may cause infertility in male subjects (low or no sperm count) and treatment with chlorambucil may result in azoospermia (complete lack of sperm). The effect of ibrutinib and obinutuzumab on sperm is unknown. Therefore, pregnancies in partners of male subjects included

in the study will be reported by the investigational staff within 24 hours of their knowledge of the event using the appropriate pregnancy notification form.

12.4. Contacting Sponsor Regarding Safety

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding safety issues or questions regarding the study are listed in the Contact Information page(s), which will be provided as a separate document.

13. PRODUCT QUALITY COMPLAINT HANDLING

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging (ie, any dissatisfaction relative to the identity, quality, durability, or reliability of a product, including its labeling or package integrity). A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information; all studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

13.1. Procedures

All initial PQCs must be reported to the sponsor by the study site personnel within 24 hours after being made aware of the event.

If the defect is combined with an SAE, the study site personnel must report the PQC to the sponsor according to the SAE reporting timelines (refer to Section 12.3.2, Serious Adverse Events). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

13.2. Contacting Sponsor Regarding Product Quality

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding product quality issues are listed in the Contact Information page(s), which will be provided as a separate document.

14. STUDY INTERVENTION INFORMATION

Throughout this section, “study drug” will refer to I+VEN, and study treatment will refer to ibrutinib, venetoclax, obinutuzumab, and chlorambucil. Refer to the SIPPM for additional guidance on study drug storage, preparation, and handling.

14.1. Physical Description of Study Interventions

The ibrutinib is supplied as a gray, size 0, hard gelatin capsule containing 140 mg of ibrutinib. All formulation excipients are compendial and are commonly used in oral formulations. It will be manufactured and provided under the responsibility of the sponsor. Refer to the ibrutinib IB for a list of excipients.

Venetoclax tablets are provided as film coated tablets in blister packs. Venetoclax 10 mg, 50 mg, and 100 mg will be provided by the sponsor.

Obinutuzumab is supplied as 1000 mg/40 mL (25 mg/mL) single-dose vials. Obinutuzumab 1000 mg will be provided by the sponsor.

Chlorambucil is supplied as brown, biconvex tablets containing 2 mg chlorambucil in amber glass bottles with child-resistant closures. Chlorambucil 2 mg will be provided by the sponsor.

14.2. Packaging

All study drug will have labels bearing the appropriate label text as required by governing regulatory agencies.

The ibrutinib capsules will be packaged in opaque high-density polyethylene plastic bottles. Ibrutinib capsules are supplied in a bottle with a child-resistant closure.

Venetoclax 10 mg, 50 mg, and 100 mg will be packaged in child-resistant dosepaks.

Obinutuzumab 1000 mg will be packaged as a single non-child-resistant vial.

Chlorambucil 2 mg will be packaged as 1 child-resistant bottle.

14.3. Labeling

Study treatment labels will contain information to meet the applicable regulatory requirements.

14.4. Preparation, Handling, and Storage

The recommended storage condition for ibrutinib capsules is room temperature (15°C to 30°C) (59°F to 86°F). Refer to the SIPPM for additional guidance on study drug preparation and handling.

Venetoclax, obinutuzumab, and chlorambucil should be stored according to the conditions as instructed on the drug label.

The study treatment must be stored in a secure area and administered only to subjects entered into the clinical study in accordance with the conditions specified in this protocol. Study site personnel will instruct subjects on how to store study medications for at-home use as indicated for this protocol. Subjects should be advised to keep all study medications out of reach and sight of children.

14.5. Intervention Accountability

The investigator is responsible for ensuring that all study treatment received at the site is inventoried and accounted for throughout the study. The dispensing of study medications to the subject, and the return of these study medications from the subject (if applicable), must be documented on the drug accountability form. Subjects must be instructed to return all original containers, whether empty or containing study medication. All study treatment will be stored and

disposed of according to the sponsor's instructions. Site staff must not combine contents of the study treatment containers.

Study treatment must be handled in strict accordance with the protocol and the container label and must be stored at the study site in a limited-access area or in a locked cabinet under appropriate environmental conditions. Unused study treatment including that returned by the subject, must be available for verification by the sponsor's site monitor during on-site monitoring visits. The return to the sponsor of unused oral study treatment, or used returned study medication for destruction, will be documented on the drug return form. When the site is an authorized destruction unit and study treatment supplies are destroyed on site, this must also be documented on the drug return form.

Potentially hazardous materials such as used ampules, needles, syringes and vials containing hazardous liquids, should be disposed of immediately in a safe manner and therefore will not be retained for drug accountability purposes.

Study treatments should be dispensed under the supervision of the investigator or a qualified member of the investigational staff, or by a hospital/clinic pharmacist. Study treatments will be supplied only to subjects participating in the study. Returned study treatments must not be dispensed again, even to the same subject. Study treatment may not be relabeled or reassigned for use by other subjects. The investigator agrees neither to dispense the study treatment from, nor store it at, any site other than the study sites agreed upon with the sponsor.

15. STUDY-SPECIFIC MATERIALS

The investigator will be provided with the following supplies:

- Study Protocol
- Subject study tools (diary card, emergency ID card etc, as applicable per country)
- Investigator study tools and quick reference cards
- Ibrutinib IB
- Package inserts for venetoclax, chlorambucil, and obinutuzumab
- Trial Center File, and corresponding site-specific documentation
- SIPPM and Site Investigational Product Binder
- Laboratory Manual and laboratory kits
- Imaging Site Operations Manual and Image Acquisition Guidelines
- NCI-CTCAE Version 4.03
- PRO questionnaires and user manuals: PRO questionnaires will include the EORTC QLQ-C30, EQ-5D-5L and the FACIT-Fatigue scale. The data collection format will be an electronic tablet. The format will be pre-programmed and subjects will make their responses directly on the tablet. Sample questionnaires are provided in Attachment 11, Attachment 12, and Attachment 13, but should not be used for collection of subject data.

- IWRS Manual
- eCRF Completion Guidelines

16. ETHICAL ASPECTS

16.1. Study-specific Design Considerations

This is a randomized, open-label, multicenter Phase 3 study to compare the efficacy and safety of I+VEN compared with the standard of care therapy G-Clb in subjects with newly diagnosed CLL who are not suitable for fludarabine-based regimens. All subjects will receive active treatment (either I+VEN or G-Clb). G-Clb was chosen as the comparator for this study on the basis of its efficacy and safety, and because it is a standard of care regimen with fixed-duration regimen which is recommended by both US and EU treatment guidelines for use in this subject population.[15,16,18,40] While the G-Clb regimen is the current standard of care for patients with previously untreated CLL, the median PFS is less than 3 years. The rationale for the combination of I+VEN is supported by their complementary mechanisms of action and preclinical and clinical data showing its potential for deep, durable, MRD-negative responses which is anticipated to result in prolonged PFS (Section 1.5). Though each treatment has a different approach to therapy (eg, intravenous, cytotoxic drugs for 6 months versus oral, targeted therapies for 15 months), there is sufficient rationale for the I+VEN combination.

Subjects who initially responded to fixed-duration treatment with I+VEN are expected to retain sensitivity to ibrutinib, supporting the use of the same agent after disease relapse. For subjects previously treated with G-Clb, single-agent ibrutinib is an appropriate and approved second-line treatment option.

All participating subjects will receive supportive care and will be followed closely for safety and efficacy throughout the study. Efficacy assessments will occur according to the internationally accepted response criteria from the 2008 iwCLL Guidelines. Safety assessments, including laboratory tests, will occur through regular clinic visits.

Potential subjects will be fully informed of the risks and requirements of the study. During the study, enrolled subjects will be given any new information that may affect their decision to continue participation. They will be informed that their consent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only subjects who are fully able to understand the risks, benefits, and potential AEs of the study, and provide their consent voluntarily will be enrolled.

Subjects assigned to Treatment Arm A will have a maximum of approximately 508 mL of blood collected during the treatment period. Subjects assigned to Treatment Arm B will have a maximum of approximately 323 mL of blood collected during the treatment period. After the treatment period, approximately 34 to 84 mL of blood will be collected yearly in both treatment groups. During the Subsequent Therapy Phase, a maximum of approximately 176 mL will be collected during the first year of participation. Thereafter, a maximum of approximately 92 mL will be collected each subsequent year on treatment. This includes laboratory assessments

associated with treatment, efficacy assessments (eg, MRD sampling), biomarker samples, and pharmacokinetic samples for subjects in Treatment Arm A. The volume of blood to be drawn is considered to be normal and acceptable for subjects participating in a cancer clinical study and is deemed reasonable over the time frame of the study.

16.2. Regulatory Ethics Compliance

16.2.1. Investigator Responsibilities

The investigator is responsible for ensuring that the study is performed in accordance with the protocol, current ICH guidelines on Good Clinical Practice (GCP), and applicable regulatory and country-specific requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study subjects are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible.

16.2.2. Independent Ethics Committee or Institutional Review Board

Before the start of the study, the investigator (or sponsor where required) will provide the IEC/IRB with current and complete copies of the following documents (as required by local regulations):

- Final protocol and, if applicable, amendments
- Sponsor-approved ICF (and any other written materials to be provided to the subjects)
- IB (or equivalent information) and amendments/addenda
- Sponsor-approved subject recruiting materials
- Information on compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- Investigator's curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB)
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for subjects
- Any other documents that the IEC/IRB requests to fulfill its obligation.

This study will be undertaken only after the IEC/IRB has approved of the final protocol, amendments (if any, excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct, unless required locally), the ICF, applicable recruiting materials, and subject compensation programs, and the sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

During the study, the investigator (or sponsor where required) will send the following documents and updates to the IEC/IRB for their review and approval, where appropriate:

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct)
- Revision(s) to ICF and any other written materials to be provided to subjects
- If applicable, new or revised subject recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- New edition(s) of the IB and amendments/addenda
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of AEs that are serious, unlisted/unexpected, and associated with the study intervention
- New information that may adversely affect the safety of the subjects or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the subjects
- Report of deaths of subjects under the investigator's care
- Notification if a new investigator is responsible for the study at the site
- Development Safety Update Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB.

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data, or study conduct), the amendment and applicable ICF revisions must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).

At least once a year, the IEC/IRB will be asked to review and reapprove this study, where required.

At the end of the study, the investigator (or sponsor where required) will notify the IEC/IRB about the study completion.

16.2.3. Informed Consent

Each subject must give written consent according to local requirements after the nature of the study has been fully explained. The ICF must be signed before performance of any study-related activity. The ICF that is used must be approved by both the sponsor and by the reviewing IEC/IRB and be in a language that the subject can read and understand. The ICF should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

Before enrollment in the study, the investigator or an authorized member of the study site personnel must explain to potential subjects the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Subjects will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the subject will receive for the treatment of his or her disease. Subjects will be told that alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment. Finally, they will be told that the investigator will maintain a subject identification register for the purposes of long-term follow-up if needed and that their records may be accessed by health authorities and authorized sponsor staff without violating the confidentiality of the subject, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the subject is authorizing such access, and agrees to allow his or her study physician to recontact the subject for the purpose of obtaining consent for additional safety evaluations, if needed, and subsequent disease-related treatments, or to obtain information about his or her survival status.

The subject will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of the subject's personally dated signature. After having obtained the consent, a copy of the ICF must be given to the subject.

If the subject is unable to read or write, an impartial witness should be present for the entire informed consent process (which includes reading and explaining all written information) and should personally date and sign the ICF after the oral consent of the subject is obtained.

16.2.4. Privacy of Personal Data

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of subjects confidential.

The informed consent obtained from the subject includes explicit consent for the processing of personal data and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries.

The subject has the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

Exploratory DNA and biomarker research is not conducted under standards appropriate for the return of data to subjects. In addition, the sponsor cannot make decisions as to the significance of any findings resulting from exploratory research. Therefore, exploratory research data will not be returned to subjects or investigators, unless required by law or local regulations. Privacy and confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.

16.2.5. Long-Term Retention of Samples for Additional Future Research

Samples collected in this study may be stored for up to 15 years after end of study (or according to local regulations) for additional research. Samples will only be used to understand ibrutinib and venetoclax, to understand CLL, to understand differential intervention responders, and to develop tests/assays related to ibrutinib and venetoclax and CLL. The research may begin at any time during the study or the post-study storage period.

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Subjects may withdraw their consent for their samples to be stored for research (refer to Section 10.4).

16.2.6. Country Selection

This study will only be conducted in those countries where the intent is to launch or otherwise help ensure access to the developed product if the need for the product persists, unless explicitly addressed as a specific ethical consideration in Section 16.1.

17. ADMINISTRATIVE REQUIREMENTS

17.1. Protocol Amendments

Neither the investigator nor the sponsor will modify this protocol without a formal amendment by the sponsor. All protocol amendments must be issued by the sponsor and signed and dated by the investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the subjects, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the sponsor. When the change(s) involves only logistic or administrative aspects of the study, the IEC/IRB (where required) only needs to be notified.

During the course of the study, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate sponsor representative listed in the Contact Information page(s), which will be provided as a separate document. Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the eCRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

17.2. Regulatory Documentation

17.2.1. Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country, if applicable. A study may not be initiated until all local regulatory requirements are met.

17.2.2. Required Prestudy Documentation

The following documents must be provided to the sponsor before shipment of study intervention to the study site:

- Protocol and amendment(s), if any, signed and dated by the principal investigator
- A copy of the dated and signed (or sealed, where appropriate per local regulations), written IEC/IRB approval of the protocol, amendments, ICF, any recruiting materials, and if applicable, subject compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed (or sealed, where appropriate per local regulations) by the chairman or authorized designee.
- Name and address of the IEC/IRB, including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the study site personnel is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.
- Regulatory authority approval or notification, if applicable
- Signed and dated statement of investigator (eg, Form FDA 1572), if applicable
- Documentation of investigator qualifications (eg, curriculum vitae)
- Completed investigator financial disclosure form from the principal investigator, where required
- Signed and dated Clinical Trial Agreement, which includes the financial agreement
- Any other documentation required by local regulations.

The following documents must be provided to the sponsor before enrollment of the first subject:

- Completed investigator financial disclosure forms from all subinvestigators
- Documentation of sub-investigator qualifications (eg, curriculum vitae)
- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests, if applicable
- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable.

17.3. Subject Identification, Enrollment, and Screening Logs

The investigator agrees to complete a subject identification and enrollment log to permit easy identification of each subject during and after the study. This document will be reviewed by the sponsor study site contact for completeness.

The subject identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure subject confidentiality, no copy will be made. All reports and communications relating to the study will identify subjects by subject identification and date of birth (as allowed by local regulations). In cases where the subject is not randomized into the study, the date seen and date of birth (as allowed by local regulations) will be used.

The investigator must also complete a subject screening log, which reports on all subjects who were seen to determine eligibility for inclusion in the study.

17.4. Source Documentation

At a minimum, source documents consistent in the type and level of detail with that commonly recorded at the study site as a basis for standard medical care must be available for the following: subject identification, eligibility, and study identification; study discussion and date of signed informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all AEs and follow-up of AEs; concomitant medication; intervention receipt/dispensing/return records; study intervention administration information; and date of study completion and reason for early discontinuation of study intervention or withdrawal from the study, if applicable.

The author of an entry in the source documents should be identifiable.

At a minimum, the type and level of detail of source data available for a study subject should be consistent with that commonly recorded at the site as a basis for standard medical care. Specific details required as source data for the study and source data collection methods will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

Subject-completed scales and assessments designated by the sponsor (PRO questionnaires) will be recorded directly into an electronic device and will be considered source data.

An electronic source system may be utilized, which contains data traditionally maintained in a hospital or clinic record to document medical care (eg, electronic source documents) as well as the clinical study-specific data fields as determined by the protocol. This data is electronically extracted for use by the sponsor. If the electronic source system is utilized, references made to the eCRF in the protocol include the electronic source system but information collected through the electronic source system may not be limited to that found in the eCRF. Data in this system may be considered source documentation.

17.5. Case Report Form Completion

Case report forms are provided for each subject in electronic format. All eCRF entries, corrections, and alterations must be made by the investigator or other authorized study site personnel. The investigator must confirm that all data entries in the eCRFs are accurate and correct.

Electronic data capture (eDC) will be used for this study. The study data will be transcribed by study site personnel from the source documents onto an electronic eCRF and transmitted in a secure manner to the sponsor within the timeframe agreed upon between the sponsor and the site. The electronic file will be considered to be the eCRF.

Worksheets may be used for the capture of some data to facilitate completion of the eCRF. Any such worksheets will become part of the subject's source documentation. All data relating to the study must be recorded in eCRFs prepared by the sponsor. Data must be entered into eCRFs in English. Designated site personnel must complete the eCRF within the timelines specified by the site contract after a subject visit, and the forms should be available for review at the next scheduled monitoring visit.

If necessary, queries will be generated in the eDC tool. If corrections to a eCRF are needed after the initial entry into the eCRF, then this can be done in either of the following ways:

- Investigator and study site personnel can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool)
- Site manager or clinical data manager can generate a query for resolution by the investigator and study site personnel

17.6. Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and associated personnel before the study, periodic monitoring visits by the sponsor, and direct transmission of clinical laboratory data from a central laboratory into the sponsor's database. Written instructions will be provided for collection, preparation, and shipment of samples.

Guidelines for eCRF completion will be provided and reviewed with study personnel before the start of the study.

The sponsor will review eCRFs for accuracy and completeness during on-site monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the clinical study database they will be verified for accuracy and consistency with the data sources.

17.7. Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all eCRF and all source documents that support the data collected from each subject, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the sponsor.

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this study, the investigator/institution must permit access to such reports.

17.8. Monitoring

The sponsor will use a combination of monitoring techniques: central, remote and on-site monitoring to monitor this study.

The sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study site visit log that will be kept at the study site. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare the data entered into the eCRF with the source documents (eg, hospital/clinic/physician’s office medical records). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the eCRF are known to the sponsor and study site personnel and are accessible for verification by the sponsor study site contact. If electronic records are maintained at the study site, the method of verification must be discussed with the study site personnel.

Direct access to source documents (medical records) must be allowed for the purpose of verifying that the recorded data are consistent with the original source data. Findings from this review will be discussed with the study site personnel. The sponsor expects that, during monitoring visits, the relevant study site personnel will be available, the source documents will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

In addition to on-site monitoring visits, remote contacts can occur. It is expected that during these remote contacts, study site personnel will be available to provide an update on the progress of the study at the site.

Central monitoring will take place for data identified by the sponsor as requiring central review.

17.9. Study Completion/Termination

17.9.1. Study Completion/End of Study

The study is considered completed approximately 5 years after the last subject is randomized into the study or after 50% of the subjects have died, whichever comes first. The final data from the study site will be sent to the sponsor (or designee) after completion of the final subject assessment at that study site, in the time frame specified in the Clinical Trial Agreement.

17.9.2. Study Termination

The sponsor reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

The investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IEC/IRB or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of subjects by the investigator
- Discontinuation of further study intervention development.

17.10. On-Site Audits

Representatives of the sponsor's clinical quality assurance department may visit the study site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection. Subject privacy must, however, be

respected. The investigator and study site personnel are responsible for being present and available for consultation during routinely scheduled study site audit visits conducted by the sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The investigator should immediately notify the sponsor if he or she has been contacted by a regulatory agency concerning an upcoming inspection.

17.11. Use of Information and Publication

All information, including but not limited to information regarding ibrutinib or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data, including exploratory biomarker research data, generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study, and will not use it for other purposes without the sponsor's prior written consent.

The investigator understands that the information developed in the study will be used by the sponsor in connection with the continued development of ibrutinib, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the study.

The results of the study will be reported in a Clinical Study Report generated by the sponsor and will contain data from all study sites that participated in the study as per protocol. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator for the study. Results of exploratory biomarker analyses performed after the Clinical Study Report has been issued will be reported in a separate report and will not require a revision of the Clinical Study Report. Study subject identifiers will not be used in publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors guidelines, the sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish study site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or

regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and substudy approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 18 months after study end date, or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the International Committee of Medical Journal Editors (ICMJE) Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals, which state that the named authors must have made a significant contribution to the conception or design of the work; or the acquisition, analysis, or interpretation of the data for the work; and drafted the work or revised it critically for important intellectual content; and given final approval of the version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Registration of Clinical Studies and Disclosure of Results

The sponsor will register and disclose the existence of and the results of clinical studies as required by law.

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Attachment 1: Ibrutinib Risks

For the most comprehensive clinical safety information, please refer to the latest version of the ibrutinib IB and Addenda.

HEMATOLOGIC

Leukostasis

There were isolated cases of leukostasis reported in subjects treated with ibrutinib. A high number of circulating lymphocytes (>400,000/μL) may confer increased risk. These subjects should be closely monitored. Administer supportive care such as hydration and/or cytoreduction as indicated. Ibrutinib may be temporarily held and the medical monitor should be contacted.

Cytopenias

Treatment-emergent Grade 3 or 4 cytopenias (neutropenia, thrombocytopenia, and anemia) were reported in subjects treated with ibrutinib. Monitor CBCs monthly.

Lymphocytosis

Upon initiation of single-agent treatment with ibrutinib, a reversible increase in lymphocyte counts (ie, ≥50% increase from baseline and an absolute count >5,000/μL), often associated with reduction of lymphadenopathy, has been observed in most subjects (66%) with CLL. This observed lymphocytosis is a pharmacodynamic effect and should not be considered PD in the absence of other clinical findings. In CLL, lymphocytosis typically occurs during the first month of ibrutinib therapy and typically resolves within a median of 14 weeks.

NON-HEMATOLOGIC

Bleeding-related Events

There have been reports of bleeding events in subjects treated with ibrutinib, both with and without thrombocytopenia. These include minor bleeding events such as contusion, epistaxis, and petechiae, and major bleeding events, some fatal, including gastrointestinal bleeding, intracranial hemorrhage, and hematuria. In an in vitro platelet function study, inhibitory effects of ibrutinib on collagen-induced platelet aggregation were observed. Use of either anticoagulant or antiplatelet agents concomitantly with ibrutinib increases the risk of bleeding. A higher risk for major bleeding was observed with anticoagulant than with antiplatelet agents. Consider the risks and benefits of anticoagulant or antiplatelet therapy when co-administered with ibrutinib. Monitor for signs and symptoms of bleeding.

Ibrutinib should be held at least 3 to 7 days pre- and post-surgery, depending upon the type of surgery and the risk of bleeding. Subjects with congenital bleeding diathesis have not been studied. See Section 8.2 for guidance on concomitant use of anticoagulants, antiplatelet therapy and/or supplements. See Section 4.3 for guidance on ibrutinib management with surgeries or procedures.

Infections

Infections (including sepsis, bacterial, viral, or fungal infections) were observed in subjects treated with ibrutinib therapy. Some of these infections have been associated with hospitalization and death. Consider prophylaxis according to standard of care in subjects who are at increased risk for opportunistic infections (see Section 8.1). Although causality has not been established, cases of progressive multifocal leukoencephalopathy and Hepatitis B reactivation have occurred in subjects treated with ibrutinib. Subjects should be monitored for signs and symptoms (fever, chills, weakness, confusion, vomiting, and jaundice), and appropriate therapy should be instituted as indicated.

Interstitial Lung Disease

Cases of interstitial lung disease (ILD) have been reported in subjects treated with ibrutinib. Monitor subjects for pulmonary symptoms indicative of ILD. If symptoms develop, follow the protocol dose modification guidelines (see Section 6.1.1.2). If symptoms persist, consider the risks and benefits of ibrutinib treatment and follow the dose modification guidelines (Section 6.1.1.2).

Cardiac Arrhythmias

Atrial fibrillation, atrial flutter, and cases of ventricular tachyarrhythmia including some fatal events, have been reported in subjects treated with ibrutinib, particularly in subjects with cardiac risk factors, hypertension, acute infections, and a previous history of cardiac arrhythmia. Periodically monitor patients clinically for cardiac arrhythmia. Subjects who develop arrhythmic symptoms (eg, palpitations, light-headedness, syncope, chest discomfort, or new onset of dyspnea) should be evaluated clinically, and if indicated, have an ECG performed. For cardiac arrhythmias which persist, consider the risks and benefits of ibrutinib treatment, and follow the protocol dose modification guidelines (see Section 6.1.1.2).

Cerebrovascular Accidents

Although causality has not been established, cases of cerebrovascular accident, transient ischemic attack, and ischemic stroke including fatalities have been reported with the use of ibrutinib in the post-marketing setting, with and without concomitant atrial fibrillation and/or hypertension. Regular monitoring and appropriate treatment of conditions that can contribute to the occurrence of these events is recommended.

Tumor Lysis Syndrome

Tumor lysis syndrome has been reported with ibrutinib therapy. Subjects at risk of tumor lysis syndrome are those with high tumor burden prior to treatment. Monitor subjects closely and take appropriate precautions.

Non-melanoma Skin Cancer

Non-melanoma skin cancers have occurred in subjects treated with ibrutinib. Monitor subjects for the appearance of non-melanoma skin cancer.

Diarrhea

Diarrhea is the most frequently reported non-hematologic AE with ibrutinib monotherapy and combination therapy. Other frequently reported gastrointestinal events include nausea, vomiting, and constipation. These events are rarely severe and are generally managed with supportive therapies including antidiarrheals and antiemetics. Subjects should be monitored carefully for gastrointestinal AEs and cautioned to maintain fluid intake to avoid dehydration. Medical evaluation should be made to rule out other etiologies such as *Clostridium difficile* or other infectious agents. Should symptoms be severe or prolonged follow the protocol dose modification guidelines (see Section 6.1.1.2).

Rash

Rash has been commonly reported in subjects treated with either single-agent ibrutinib or in combination with chemotherapy. Rash occurred at a higher rate in the ibrutinib arm than in the ofatumumab arm in Study PCYC-1112-CA. Most rashes were mild to moderate in severity. Isolated cases of severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS) have been reported in subjects treated with ibrutinib. Subjects should be closely monitored for signs and symptoms suggestive of SCAR including SJS. Subjects receiving ibrutinib should be observed closely for rashes and treated symptomatically, including interruption of the suspected agent as appropriate. In addition, hypersensitivity-related events erythema, urticaria, angioedema have been reported.

Hypertension

Hypertension has occurred in subjects treated with ibrutinib. Regularly monitor blood pressure in subjects treated with ibrutinib and initiate or adjust antihypertensive medication throughout treatment with ibrutinib as appropriate.

Attachment 2: Cumulative Illness Rating Scale (CIRS)

Please take into account that CLL-induced illness or organ damage are not included in this rating scale. The goal of this rating scale is to assess comorbidity other than CLL in the patient. If there are 2 or more illness/impairments of one organ system, the illness/impairment with the highest severity should be evaluated.

Organ system	If illness/impairment present, specify the illness/impairment with highest severity	Score
Cardiac		_____
Hypertension		_____
Vascular		_____
Respiratory		_____
Eye/ear/nose/throat/larynx		_____
Upper gastrointestinal		_____
Lower gastrointestinal		_____
Hepatic/biliary		_____
Renal		_____
Genitourinary		_____
Musculoskeletal		_____
Endocrine/metabolic		_____
Neurological		_____
Psychiatric		_____
	Total score	_____

CIRS Rating of Comorbidity

Score
0 No problem Organ system not compromised.
1 Mild Illness/impairment with or without requirement of therapy, excellent prognosis, patient with normal activity
2 Moderate Illness/impairment requiring therapy, good prognosis; compromised activity of patients
3 Severe Illness/impairment with urgent requirement for therapy, prognosis unclear, marked restriction in activity of patient.
4 Extremely severe Life-threatening illness/impairment, emergency case of therapy, adverse prognosis.

Link to Manual of Guidelines to score the modified Cumulative Illness Rating Scale:
https://onlinelibrary.wiley.com/doi/full/10.1111/j.1532-5415.2008.01935.x

Source: Salvi F, Miller MD, Grilli A, et al. A manual of guidelines to score the modified cumulative illness rating scale and its validation in acute hospitalized elderly patients. J Am Geriatr Soc. 2008;56:1926–1931.[48]

Attachment 3: Contraceptive and Barrier Guidance and Collection of Pregnancy Information

Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Woman Not of Childbearing Potential

- **premenarchal**
  A premenarchal state is one in which menarche has not yet occurred.
- **postmenopausal**
  A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level (>40 IU/L or mIU/mL) in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT), however in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient. If there is a question about menopausal status in women on HRT, the woman will be required to use one of the non-estrogen-containing hormonal highly effective contraceptive methods if she wishes to continue HRT during the study.
- **permanently sterile**
  Permanent sterilization methods include hysterectomy, bilateral salpingectomy, bilateral tubal occlusion/ligation procedures, and bilateral oophorectomy.

Note: If the childbearing potential changes after start of the study (eg, a premenarchal woman experiences menarche) or the risk of pregnancy changes (eg, a woman who is not heterosexually active becomes active), a woman must begin a highly effective method of contraception, as described throughout the inclusion criteria.

If reproductive status is questionable, additional evaluation should be considered.

Examples of Contraceptives

EXAMPLES OF CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
USER-INDEPENDENT **Highly Effective Methods That Are User-Independent** *Failure rate of ≤1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[b]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)
• Bilateral tubal occlusion
• Vasectomized partner *(Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 74 days.)*

USER DEPENDENT **Highly Effective Methods That Are User Dependent** *Failure rate of <1% per year when used consistently and correctly.*
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] – oral – intravaginal – transdermal – injectables
• Progestogen-only hormone contraception associated with inhibition of ovulation[b] – oral – injectable
• Sexual abstinence *(Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.)*
NOT ALLOWED AS SOLE METHOD OF CONTRACEPTION DURING THE STUDY (not considered to be highly effective - failure rate of >1% per year)
• Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action.
• Male or female condom with or without spermicide[c]
• Cap, diaphragm, or sponge with spermicide
• A combination of male condom with either cap, diaphragm, or sponge with spermicide (double-barrier methods)[c]
• Periodic abstinence (calendar, symptothermal, post-ovulation methods)
• Withdrawal (coitus-interruptus)
• Spermicides alone
• Lactational amenorrhea method (LAM)
a) Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for subjects participating in clinical studies. b) Hormonal contraception may be susceptible to interaction with the study intervention, which may reduce the efficacy of the contraceptive method. In addition, consider if the hormonal contraception may interact with the study intervention. c) Male condom and female condom should not be used together (due to risk of failure with friction).

Attachment 4: Child-Pugh Scores for Subjects with Chronic Liver Impairment

Measure	1 point	2 points	3 points
Total bilirubin, µmol/L (mg/dL)	<34 (<2)	34-50 (2-3)	>50 (>3)
Serum albumin, g/L (g/dL)	>35 (>3.5)	28-35 (2.8-3.5)	<28 (<2.8)
PT/INR	<1.7	1.71-2.30	>2.30
Ascites	None	Mild	Moderate to Severe
Hepatic encephalopathy	None	Grade I-II (or suppressed with medication)	Grade III-IV (or refractory)

Points	Class
5-6	A
7-9	B
10-15	C

Sources:

- [7]Child CG, Turcotte JG. "Surgery and portal hypertension". In Child CG. The liver and portal hypertension. Philadelphia: Saunders. 1964. pp. 50-64.
- [43]Pugh RN, Murray-Lyon IM, Dawson L, et al. "Transection of the oesophagus for bleeding oesophageal varices". The British journal of surgery, 1973;60: 646-649.

Attachment 5: Inhibitors and Inducers of CYP3A

The table below shows the classification of commonly used inhibitors and inducers of CYP3A enzymes. Further information can be found at the following websites: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers[13] and http://medicine.iupui.edu/clinpharm/ddis/main-table/.[12]

Inhibitors of CYP3A	Inducers of CYP3A
Strong inhibitors:	carbamazepine
Boceprevir	barbiturates
Clarithromycin	efavirenz
Cobicistat	glucocorticoids
Indinavir	modafinil
Itraconazole	nevirapine
Ketoconazole	oxcarbarzepine
Mibefradil	phenobarbital
Nefazodonene	phenytoin
Nelfinavir	pioglitazone
posaconazole	rifabutin
Ritonavir	rifampin
Saquinavir	St. John's Wort
Suboxone	troglitazone
Telaprevir	
Telithromycin	
Troleandomycin	
voriconazole	
Moderate inhibitors:	
Amiodarone	
Amprenavir	
Aprepitant	
Atazanavir	
Ciprofloxacin	
Crizotinib	
Darunavir	
diltiazem	
Dronedarone	
Erythromycin	
Fluconazole	
Fosamprenavir	
grapefruit juice	
Seville orange juice	
Verapamil	
Weak inhibitors:	
Cimetidine	
Fluvoxamine	
All other inhibitors:	
Chloramphenicol	
Delaviridine	
Gestodene	
Mifepristone	
Norfloxacin	
Norfluoxetine	
star fruit	

Attachment 6: Recommendations for Initial Management of Electrolyte Abnormalities and Prevention of Tumor Lysis Syndrome (TLS)

Section 1: First Dose of Venetoclax or Dose Escalation

- Within the first 24 hours after either the first dose or dose escalation, if any laboratory criteria below are met, the subject should be hospitalized for monitoring and the investigator notified. No additional venetoclax doses should be administered until resolution. A rapidly rising serum potassium is a medical emergency.
- Nephrology (or other acute dialysis service) should be notified (per institutional standards to ensure emergency dialysis is available) on admission for any subject hospitalized prophylactically or in response to laboratory changes.
- IV fluids (eg, day 5 1/2 normal saline) should be initiated at a rate of at least 1 mL/kg/hr rounded to the nearest 10 mL (target 150 to 200 mL/hr; not <50 mL/hr). Modification of fluid rate should also be considered for individuals with specific medical needs.
- Monitor for symptoms or signs of TLS (eg, fever, chills, tachycardia, nausea, vomiting, diarrhea, diaphoresis, hypotension, muscle aches, weakness, paresthesias, mental status changes, confusion, seizures). If any clinical features are observed, recheck potassium, phosphorus, uric acid, calcium, and creatinine.
- Vital signs should be taken at time of all blood draws or any Intervention.
- The management recommendations below focus on the minimum initial responses required. If a diagnosis of TLS is established, ongoing intensive monitoring and multi-disciplinary management will be per institutional protocols.

In addition to the recommendations in the table below:

- For potassium increase ≥0.5 mmol/L from baseline, or any value >5.0 mmol/L, recheck potassium, phosphorus, uric acid, calcium, and creatinine and follow first guideline.
- For phosphorus increase of >0.5 mg/dL AND >4.5 mg/dL, administer phosphate binder and recheck potassium, phosphorus, uric acid, calcium, and creatinine.

Abnormality	**Management Recommendations**[5,9]
Hyperkalemia (including rapidly rising potassium)	
Potassium ≥0.5 mmol/L increase from prior value (even if potassium within normal limits [WNL])	• Recheck potassium, phosphorus, uric acid, calcium, and creatinine. If further ≥0.2 mmol/L increase in potassium, but still <ULN, manage as per potassium ≥ULN. Otherwise recheck. • Resume per protocol testing if change in potassium is <0.2 mmol/L, and potassium < ULN, and no other evidence of tumor lysis. • At discretion of Investigator, may recheck prior to hospitalization. If stable or decreased, and still WNL, hospitalization is at the discretion of the Investigator. Potassium, phosphorus, uric acid, calcium, and creatinine must be rechecked within 24 hours.

Abnormality	Management Recommendations[5,9]
Potassium > upper limit of normal	• Perform STAT ECG and commence telemetry. • Nephrology notification with consideration of initiating dialysis. • Administer Kayexalate 60 g (or Resonium A 60 g). • Administer furosemide 20 mg IV × 1. • Administer calcium gluconate 100 – 200 mg/kg IV slowly if there is ECG/telemetry evidence of life-threatening arrhythmias. • Recheck potassium, phosphorus, uric acid, calcium, and creatinine. If potassium < ULN 1 hour later, repeat potassium, phosphorus, uric acid, calcium, and creatinine 1, 2 and 4 hours, if no other evidence of tumor lysis.
Potassium ≥6.0 mmol/L (6.0 mEq/L) and/or symptomatic (eg, muscle cramps, weakness, paresthesias, nausea, vomiting, diarrhea)	• Perform STAT ECG and commence telemetry. • Nephrology (or other acute dialysis service) notified with consideration of initiating dialysis. • Administer Kayexalate 60 g (or Resonium A 60 g). • Administer furosemide 20 mg IV × 1. • Administer insulin 0.1 U/kg IV + D25 2 mL/kg IV. • Administer sodium bicarbonate 1 to 2 mEq/kg IV push. If sodium bicarbonate is used, rasburicase should not be used as this may exacerbate calcium phosphate precipitation. • Administer calcium gluconate 100 to 200 mg/kg IV slowly if there is ECG/telemetry evidence of life-threatening arrhythmias. Do not administer in same IV line as sodium bicarbonate. • Recheck potassium, phosphorus, uric acid, calcium, and creatinine.
Hyperuricemia	
Uric acid ≥8.0 mg/dL (476 µmol/L)	• Consider rasburicase (0.2 mg/kg as an intravenous infusion over 30 minutes). If rasburicase is used, sodium bicarbonate should not be used as this may exacerbate calcium phosphate precipitation. • Recheck potassium, phosphorus, uric acid, calcium, and creatinine.
Uric acid ≥10 mg/dL (595 µmol/L) OR Uric acid ≥8.0 mg/dL (476 µmol/L) with 25% increase and creatinine increase ≥0.3 mg/dL (≥0.027mmol/L) from predose level	• Administer rasburicase (0.2 mg/kg as an intravenous infusion over 30 minutes). When rasburicase is used, sodium bicarbonate should not be used as this may exacerbate calcium phosphate precipitation. • Notify nephrology (or other acute dialysis service). • Recheck potassium, phosphorus, uric acid, calcium, and creatinine. • If uric acid < 8.0 mg/dL 1 hour later, repeat potassium, phosphorus, uric acid, calcium, and creatinine 2 and 4 hours later, if no other evidence of tumor lysis.
Hypocalcemia	
Calcium ≤ 7.0 mg/dL (1.75 mmol/L) AND Subject symptomatic (eg, muscle cramps, hypotension, tetany, cardiac arrhythmias)	• Administer calcium gluconate 50 to 100 mg/kg IV slowly with ECG monitoring. • Telemetry. • Recheck potassium, phosphorus, uric acid, calcium, and creatinine. • If calcium normalized 1 hour later, repeat potassium, phosphorus, uric acid, calcium, and creatinine 2 and 4 hours later, if no other evidence of tumor lysis. • Calculate corrected calcium and check ionized calcium if albumin low

Abnormality	Management Recommendations[5,9]
Hyperphosphatemia	
Phosphorus ≥5.0 mg/dL (1.615 mmol/L) with ≥0.5 mg/dL (0.16 mmol/L) increase	• Administer a phosphate binder (eg, aluminum hydroxide, calcium carbonate, sevelamer hydroxide, or lanthanum carbonate). • Nephrology (or other acute dialysis service) notification (dialysis required for phosphorus ≥10 mg/dL). • Recheck potassium, phosphorus, uric acid, calcium, and creatinine. • If phosphorus <5.0 mg/dL 1 hour later, repeat potassium, phosphorus, uric acid, calcium, and creatinine 2 and 4 hours later, if no other evidence of tumor lysis.
Creatinine	
Increase ≥25% from baseline	• Start or increase rate of IV fluids. • Recheck potassium, phosphorus, uric acid, calcium, and creatinine.

Section 2: Ongoing Dosing of Venetoclax

Management of electrolyte changes from last value at intervals >24 hours after either the first dose or dose escalation (eg, 48 or 72 hours) are as below.

***Note*:** If the subject is hospitalized, no additional venetoclax doses should be administered until resolution.

- For potassium, admit subject for any increase ≥1.0 mmol/L (1.0 mEq/L), or any level > ULN.
    - Refer to the management guidelines for electrolyte changes observed within the first 24 hours after either the first dose or dose escalation (see table above).
- If a smaller potassium increase is observed that does not meet the criteria for admission above, recheck potassium, phosphorus, uric acid, calcium, and creatinine in 24 hours and confirm no evidence of tumor lysis prior to further venetoclax dosing.
- For uric acid, calcium, phosphorus and creatinine, refer to the management guidelines for electrolyte changes observed within the first 24 hours after either the first dose or dose escalation (see table above).

Sources

[9]Coiffier B, Altman A, Pui CH, et al. Guidelines for the management of pediatric and adult tumor lysis syndrome: an evidence-based review. J Clin Oncol.2008;26(16):2767-78.

[5]Cairo MS, Bishop M. Tumour lysis syndrome: new therapeutic strategies and classification. Br J Haematol. 2004;127(1):3-11.

Attachment 7: Howard Criteria for Laboratory and Clinical Tumor Lysis Syndrome*

Metabolic Abnormality	Criteria for Classification of Laboratory Tumor Lysis Syndrome	Criteria for Classification of Clinical Tumor Lysis Syndrome
Hyperuricemia	Uric acid >8.0 mg/dL (475.8 µmol/liter) in adults or above the upper limit of the normal range for age in children	
Hyperphosphatemia	Phosphorus >4.5 mg/dL (1.5 mmol/liter) in adults or >6.5 mg/dL (2.1 mmol/liter) in children	
Hyperkalemia	Potassium >6.0 mmol/liter	Cardiac dysrhythmia or sudden death probably or definitely caused by hyperkalemia
Hypocalcemia	Corrected calcium <7.0 mg/dL (1.75 mmol/liter) or ionized calcium <1.12 (0.3 mmol/liter)†	Cardiac dysrhythmia, sudden death, seizure, neuromuscular irritability (tetany, paresthesias, muscle twitching, carpopedal spasm, Trousseau's sign, Chvostek's sign, laryngospasm, or bronchospasm), hypotension, or heart failure probably or definitely caused by hypocalcemia
Acute kidney injury‡	Not applicable	Increase in the serum creatinine level of 0.3 mg/dL (26.5 µmol/liter) (or a single value >1.5 times the upper limit of the age-appropriate normal range if no baseline creatinine measurement is available) or the presence of oliguria, defined as an average urine output of <0.5 mL/kg/hr for 6 hr

* In laboratory TLS, 2 or more metabolic abnormalities must be present during the same 24-hour period within 3 days before the start of therapy or up to 7 days afterward. Clinical TLS requires the presence of laboratory TLS plus an increased creatinine level, seizures, cardiac dysrhythmia, or death.

† The corrected calcium level in milligrams per deciliter=measured calcium level in milligrams per deciliter + 0.8 × (4 − albumin in grams per deciliter).

‡ Acute kidney injury is defined as an increase in the creatinine level of at least 0.3 mg per deciliter (26.5 µmol per liter) or a period of oliguria lasting 6 hours or more. By definition, if acute kidney injury is present, the patient has clinical TLS. Data about acute kidney injury are from Levin A, Warnock DG, Mehta RL, et al. Improving outcomes from acute kidney injury: report of an initiative. Am J Kidney Dis. 2007;50:1–4.

Source: [36]Howard SC, Jones DP, Pui CH. The tumor lysis syndrome. N Engl J Med. 2011;364:1844-1854.

Attachment 8: Obinutuzumab Premedication for Infusion Reactions and Tumor Lysis Syndrome

Obinutuzumab Premedication for Infusion Reactions

Obinutuzumab can cause severe and life-threatening infusion reactions. Symptoms of infusion reactions may include hypotension, tachycardia, dyspnea, and respiratory symptoms (eg, bronchospasm, larynx and throat irritation, wheezing, laryngeal edema). All subjects should be premedicated to reduce the risk of infusion reactions. Recommended premedications are summarized in table below. Because hypotension may occur during obinutuzumab infusion, consider withholding antihypertensive treatments for 12 hours prior to and throughout each obinutuzumab infusion and for the first hour after administration.

Premedication Before Obinutuzumab Infusion

Day of Treatment Cycle	Subjects requiring premedication	Premedication	Administration
Cycle 1, Day 1	All subjects	Intravenous corticosteroid[1] (mandatory)	Completed at least 1 hour prior to obinutuzumab infusion.
		Oral analgesic/anti-pyretic[2]	At least 30 minutes before obinutuzumab infusion.
		Anti-histamine medicine[3]	
Cycle 1, Day 2	All subjects	Intravenous corticosteroid[1] (mandatory)	Completed at least 1 hour prior to obinutuzumab infusion.
		Oral analgesic/anti-pyretic[2]	At least 30 minutes before obinutuzumab infusion.
		Anti-histamine medicine[3]	
All subsequent infusions	Subjects with no IRR during the previous infusion	Oral analgesic/anti-pyretic[2]	At least 30 minutes before obinutuzumab infusion.
	Subjects with an IRR (Grade 1 -2) with the previous infusion	Oral analgesic/anti-pyretic[2] Anti-histamine medicine[3]	
	Subjects with a Grade 3 IRR with the previous infusion OR Patients with lymphocyte counts >25 x 10^9/L prior to next treatment	Intravenous corticosteroid[1]	Completed at least 1 hour prior to obinutuzumab infusion.
		Oral analgesic/anti-pyretic[2] Anti-histamine medicine[3]	At least 30 minutes before obinutuzumab infusion.

1 *100 mg prednisone/prednisolone or 20 mg dexamethasone or 80 mg methylprednisolone. Hydrocortisone should not be used as it has not been effective in reducing rates of IRR.*
2 eg, *1,000 mg acetaminophen/paracetamol*
3 eg, *50 mg diphenhydramine*

Obinutuzumab Premedication for Tumor Lysis Syndrome

Subjects with high tumor burden, high circulating ALCs (>25 x 10^9/L) or renal impairment (CrCl <70 mL/min) are considered at risk for TLS and should be premedicated with anti-hyperurecemics (eg, allopurinol and/or rasburicase) and adequately hydrated 12-24 hours prior to obinutuzumab therapy. Prophylaxis should be continued prior to each infusion, as needed.

Attachment 9: Medications to be Used with Precaution with Ibrutinib and Venetoclax

CYP3A Inhibitors/Inducers

Management of Potential Ibrutinib and Venetoclax Interactions with CYP3A Inhibitors

	Venetoclax		**Ibrutinib**
Inhibitors	Initiation and Ramp-up Phase	Steady Daily Dose (After Ramp-up Phase)	At any time
Strong CYP3A Inhibitor	Contraindicated	Avoid inhibitor use, consider alternate. If must be used, reduce the venetoclax dose by at least 75%	Avoid inhibitor use, consider alternative agent. If must be used, withhold ibrutinib for duration of inhibitor use, or reduce ibrutinib to 140 mg
Moderate CYP3A Inhibitor	Avoid inhibitor use, consider alternative agent. If must be used, reduce the venetoclax dose by at least 50%		Avoid inhibitor use, consider alternative agent. If must be used, reduce ibrutinib to 280 mg

Avoid concomitant use of strong CYP3A inducers (eg, carbamazepine, rifampin, phenytoin, and St. John's Wort). Consider alternative agents with less CYP3A induction.

A list of common CYP3A inhibitors and inducers is provided in Attachment 5.

Drugs That May Have Their Plasma Concentrations Altered by Ibrutinib

In vitro studies indicated that ibrutinib is not a substrate of P-glycoprotein (P-gp), but is a mild inhibitor. Ibrutinib is not expected to have systemic drug-drug interactions with P-gp substrates. However, it cannot be excluded that ibrutinib could inhibit intestinal P-gp after a therapeutic dose. There is no clinical data available. Therefore, to avoid a potential interaction in the gastrointestinal tract, narrow therapeutic range P-gp substrates such as digoxin, should be taken at least 6 hours before or after ibrutinib.

Drugs That May Have Their Plasma Concentrations Altered by Venetoclax

Venetoclax is a P-gp and BCRP substrate as well as a P-gp and BCRP inhibitor and weak OATP1B1 inhibitor in vitro. To avoid a potential interaction in the gastrointestinal tract, co-administration of narrow therapeutic index P-gp substrates such as digoxin with venetoclax should be avoided. If a narrow therapeutic index P-gp substrate must be used, it should be taken at least 6 hours before venetoclax.

Antiplatelet Agents and Anticoagulants

Ibrutinib

Warfarin or other vitamin K antagonists should not be administered concomitantly with ibrutinib. Supplements such as fish oil and vitamin E preparations should be avoided during treatment with ibrutinib. Use ibrutinib with caution in subjects requiring anticoagulants or medications that inhibit platelet function. Ibrutinib should be held at least 3 to 7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding (see Section 4.3). Subjects with congenital bleeding diathesis have not been studied.

Subjects requiring the initiation of therapeutic anticoagulation therapy (other than warfarin or a vitamin K antagonist) during the course of the study should be discussed with the medical monitor. If therapeutic anticoagulation is clinically indicated, treatment with ibrutinib should be held and not be restarted until the subject is clinically stable and has no signs of bleeding. Subjects should be observed closely for signs and symptoms of bleeding, and the risks and benefits of continuing ibrutinib treatment should be considered. No dose reduction is required when study drug is restarted.

Venetoclax

In a drug-drug interaction study in healthy subjects, administration of a single dose of venetoclax with warfarin resulted in an 18% to 28% increase in C_{max} and area under the concentration-time curve to infinity of R-warfarin and S-warfarin. Because venetoclax was not dosed to steady-state, it is recommended that the INR be monitored closely in subjects receiving warfarin.

Attachment 10: CLL and SLL Staging Criteria

Rai Staging System

Stage 0

Stage 0 CLL is characterized by absolute lymphocytosis (>15,000/mm^3) without adenopathy, hepatosplenomegaly, anemia, or thrombocytopenia.

Stage I

Stage I CLL is characterized by absolute lymphocytosis with lymphadenopathy without hepatosplenomegaly, anemia, or thrombocytopenia.

Stage II

Stage II CLL is characterized by absolute lymphocytosis with either hepatomegaly or splenomegaly with or without lymphadenopathy.

Stage III

Stage III CLL is characterized by absolute lymphocytosis and anemia (hemoglobin <11 g/dL) with or without lymphadenopathy, hepatomegaly, or splenomegaly.

Stage IV

Stage IV CLL is characterized by absolute lymphocytosis and thrombocytopenia (<100,000/mm^3) with or without lymphadenopathy, hepatomegaly, splenomegaly, or anemia.

Binet Classification

Clinical Stage A*

Clinical stage A CLL is characterized by no anemia or thrombocytopenia and fewer than 3 areas of lymphoid involvement (Rai stages 0, I, and II).

Clinical Stage B*

Clinical stage B CLL is characterized by no anemia or thrombocytopenia with 3 or more areas of lymphoid involvement (Rai stages I and II).

Clinical Stage C

Clinical stage C CLL is characterized by anemia and/or thrombocytopenia regardless of the number of areas of lymphoid enlargement (Rai stages III and IV).

*[Note: Lymphoid areas include cervical, axillary, inguinal, and spleen.]

The Ann Arbor SLL Staging System with Cotswold's Modifications

Stage I: Involvement of a single lymph node region (eg, cervical, axillary, inguinal, mediastinal) or lymphoid structure such as the spleen, thymus, or Waldeyer's ring.

Stage II: Involvement of 2 or more lymph node regions or lymph node structures on the same side of the diaphragm. Hilar nodes should be considered to be "lateralized" and when involved on both sides, constitute Stage II disease. For the purpose of defining the number of anatomic regions, all nodal disease within the mediastinum is considered to be a single lymph node region, and hilar involvement constitutes an additional site of involvement. The number of anatomic regions should be indicated by a subscript (eg, II-3).

Stage III: Involvement of lymph node regions or lymphoid structures on both sides of the diaphragm. This may be subdivided stage III-1 or III-2: stage III-1 is used for patients with involvement of the spleen or splenic hilar, celiac, or portal nodes; and stage III-2 is used for patients with involvement of the para-aortic, iliac, inguinal, or mesenteric nodes.

Stage IV: Diffuse or disseminated involvement of one or more extranodal organs or tissue beyond that designated E, with or without associated lymph node involvement.

Additional notes:

- All cases are subclassified to indicate the absence (A) or presence (B) of the systemic symptoms of significant unexplained fever, night sweats, or unexplained weight loss exceeding 10% of body weight during the 6 months prior to diagnosis.
- The designation "E" refers to extranodal contiguous extension (ie, proximal or contiguous extranodal disease) that can be encompassed within an irradiation field appropriate for nodal disease of the same anatomic extent. More extensive extranodal disease is designated stage IV.
- The subscript "X" is used if bulky disease is present. This is defined as a mediastinal mass with a maximum width that is equal to or greater than one-third of the internal transverse diameter of the thorax at the level of T5/6 interspace or >10 cm maximum dimension of a nodal mass. No subscripts are used in the absence of bulk.
- Subjects can be clinically or pathologically staged. Splenectomy, liver biopsy, lymph node biopsy, and bone marrow biopsy are mandatory for the establishment of pathological stage. The pathologic stage at a given site is denoted by a subscript (eg, M=bone marrow, H=liver, L=lung, O=bone, P=pleura, and D=skin).

Source: The Ann Arbor staging system with Cotswolds modifications. *Data from Lister TA, Crowther D, Sutcliffe SB, et al., J Clin Oncol 1989; 7:1630.*

Attachment 11: EORTC QLQ-C30

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Today's date (Day, Month, Year): 31

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4

Please go on to the next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
16. Have you been constipated?	1	2	3	4
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Attachment 12: EQ-5D-5L

(English version for the UK)

Under each heading, please tick the ONE box that best describes your health TODAY

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

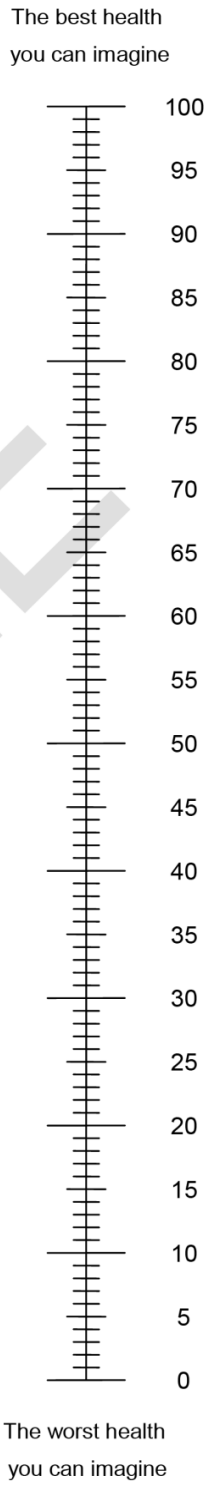
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Attachment 13: FACIT-Fatigue Scale

FACIT Fatigue Scale (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

		Not at all	A little bit	Some-what	Quite a bit	Very much
H7	I feel fatigued	0	1	2	3	4
H12	I feel weak all over	0	1	2	3	4
An1	I feel listless ("washed out")	0	1	2	3	4
An2	I feel tired	0	1	2	3	4
An3	I have trouble starting things because I am tired	0	1	2	3	4
An4	I have trouble finishing things because I am tired	0	1	2	3	4
An5	I have energy	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
An8	I need to sleep during the day	0	1	2	3	4
An12	I am too tired to eat	0	1	2	3	4
An14	I need help doing my usual activities	0	1	2	3	4
An15	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
An16	I have to limit my social activity because I am tired	0	1	2	3	4

INVESTIGATOR AGREEMENT

JNJ-54179060 (ibrutinib)
Clinical Protocol 54179060CLL3011 Amendment 4

INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study drug, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____

(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____

(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): Donne Bennett Caces, MD, PhD

Institution: Janssen Research & Development

Signature: Donne Bennett Caces Digitally signed by Donne Bennett Caces DN: c=US, o=JNJ, ou=Subscribers, 0.9.2342.19200300.100.1.1=1042388, cn=Donne Bennett Caces Reason: I am approving this document Date: 2019.12.20 07:51:13 -06'00' Adobe Acrobat version: 11.0.20 Date: _____

(Day Month Year)

Note: If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

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Approved, Date: 19 December 2019

Janssen Research & Development *

Clinical Protocol

COVID-19 Appendix

Protocol Title

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)

*Janssen Research & Development is a global organization that operates through different legal entities in various countries. Therefore, the legal entity acting as the sponsor for Janssen Research & Development studies may vary, such as, but not limited to Janssen Biotech, Inc.; Janssen Products, LP; Janssen Biologics, BV; Janssen-Cilag International NV; Janssen, Inc; Janssen Pharmaceutica NV; Janssen Sciences Ireland UC; Janssen Biopharma Inc.; or Janssen Research & Development, LLC. The term "sponsor" is used throughout the protocol to represent these various legal entities; the sponsor is identified on the Contact Information page that accompanies the protocol.

Status: Approved
Date: 24 April 2020
Prepared by: Janssen Research & Development, LLC
EDMS number: EDMS-RIM-39672, 1.0

THIS APPENDIX APPLIES TO ALL CURRENT APPROVED VERSIONS OF PROTOCOL 54179060CLL3011

GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

COVID-19 APPENDIX

GENERAL GUIDANCE ON STUDY CONDUCT DURING THE COVID-19 PANDEMIC

It is recognized that the Coronavirus Disease 2019 (COVID-19) pandemic may have an impact on the conduct of this clinical study due to, for example, self-isolation/quarantine by subjects and study-site personnel; travel restrictions/limited access to public places, including hospitals; study site personnel being reassigned to critical tasks.

In alignment with recent health authority guidance, the sponsor is providing options for study-related subject management in the event of disruption to the conduct of the study. This guidance does not supersede any local or government requirements or the clinical judgement of the investigator to protect the health and well-being of subjects and site staff. If at any time the investigator assesses that the risk of treatment may outweigh the benefits, study treatment will be interrupted, and study follow-up will be conducted.

Scheduled visits that cannot be conducted in person at the study site will be performed to the extent possible remotely/virtually or delayed until such time that on-site visits can be resumed. At each contact, subjects will be interviewed to collect safety data. Key efficacy endpoint assessments should be performed if required and as feasible. Subjects will also be questioned regarding general health status to fulfill any physical examination requirement.

Every effort should be made to adhere to protocol-specified assessments for subjects on study treatment, including follow up. Modifications to protocol-required assessments may be permitted after consultation between the subject and investigator, and with the agreement of the sponsor. Missed assessments/visits will be captured in the clinical trial management system for protocol deviations. Discontinuations of study treatment and withdrawal from the study should be documented with the prefix “COVID-19-related” in the Comments electronic case report form (eCRF).

The sponsor will continue to monitor the conduct and progress of the clinical study, and any changes will be communicated to the sites and to the health authorities according to local guidance. Modifications made to the study conduct as a result of the COVID-19 pandemic should be summarized in the clinical study report.

GUIDANCE SPECIFIC TO THIS PROTOCOL:

Subject Visits and Assessments

- For subjects who are unable to come to the site for Disease Evaluation visits, the visit should be postponed and rescheduled as soon as possible.
- For subjects who are unable to come to the site for Cycle visits, contact (eg, telephone, videoconference, or other channels) with the subject should be made in advance, to collect information on the subject's current health status and any new or ongoing adverse events and concomitant medications. The remote method that is used for contact with the subject must be allowable per local regulations and fully documented in the subject source record. Protocol-specified laboratory assessments and physical examinations should be obtained locally, if possible. Where local laboratories are used, it is important to ensure appropriate documentation of laboratory reference ranges. After reviewing all available information, and if the investigator assesses that continued treatment is acceptable, contact the site manager to discuss alternative solutions for the provision of study treatment to subjects (see alternatives below). The remote contact with the subject, the local laboratory results, and the sponsor discussion should be documented in the subject source record. Similarly, at a minimum, a comment must be entered in the Comments eCRF clearly designating as "COVID-19-related" and acknowledging the discussion between the investigator and the sponsor.
- If the subject is not willing or able to go to a local clinic/laboratory, remote contact (eg, telephone, videoconference, or other channels) with the subject is recommended, as well as a thorough review of the subject's medical history, prior labs, and most recent disease evaluation. The remote method chosen must be allowable per local regulations and fully documented in the subject source record. If appropriate, treatment should be interrupted until new laboratory assessments are made. However, if the investigator assesses that continued treatment is acceptable despite the absence of new laboratory tests, contact the site manager to discuss alternative solutions for the provision of study medication to subjects (see possible alternatives below). Proper documentation of all discussions and decisions should be made in the subject source record and in the Comments eCRF.
- If any change in subject status is identified that may impact the subject's safety, then study treatment should be interrupted until the subject can be assessed. Any changes in study treatment (dose, frequency, interruption) needs to be clearly documented as "COVID-19-related". When pandemic conditions improve, travel restrictions are lifted, and the subject is willing and able to come to the clinic, subjects should be scheduled for an in-clinic, follow-up visit.
- All deviations from protocol-required assessments should be documented in detail within the subject's source record and should be clearly designated as "COVID-19-related". It must be documented if a visit is conducted remotely. Source documentation should detail how each assessment was collected (eg, remote vs. on-site, central vs. local laboratory, vital signs taken at home by caretaker vs. delegated in-home nursing).

Study Drug Supply

If a subject is unable to travel to the site for a scheduled visit where study drug would be dispensed, the following alternate measures should be discussed with the study monitor and may be considered to ensure continuity of treatment, upon sponsor's approval:

- A caregiver or family member may pick up study drug on behalf of the subject if first discussed and agreed by the subject. The conversation with the subject must be documented in the subject source records. The subject must name the individual who will pick up study drug on their behalf. This is necessary for site staff to confirm the study drug is provided to the appropriate individual, ensure proper chain of custody of study drug, and to maintain subject privacy. Identification of who will pick up the study drug must be confirmed and documented in the subject source record.
- Investigative site staff may deliver study drug directly to the subject's home. The chain of custody and transit conditions must be clearly documented within the subject source record.
- If no other alternative is feasible, direct-to-patient shipment of study drug from the site may be considered with prior approval from the sponsor. Site staff need to obtain permission from the subject and record this in the subject source record for direct-to-patient shipments. It is important to note this process is not allowed by the health authorities in all countries and a specific approval process must be followed with the sponsor before moving forward. If requested by the site, the sponsor will investigate local requirements and confirm health authority requirements for direct-to-patient shipment. If approval is granted by the sponsor, specific procedures including shipment conditions, preferred courier services, and documentation requirements will be communicated by the sponsor to the site.

If a subject is able to come to the site for a Cycle visit but anticipates being unable to come to the next Cycle visit, the investigator may dispense study treatment for the current cycle and an additional cycle, after agreement with the sponsor's medical monitor. Prior to continuing treatment with the additional study treatment, the subject should obtain protocol-specified laboratory assessments and physical examinations locally, if possible, and the investigator should conduct a remote contact as described above. After reviewing all available information, if the investigator assesses that continued treatment is acceptable, the subject may continue treatment using the previously supplied additional study treatment. Proper documentation of all discussions and decisions should be made in the subject source record and in the Comments eCRF.

For subjects who have reason to believe they have been exposed to COVID-19 but do not yet have a confirmed diagnosis and/or are not showing symptoms of infection:

- The investigator should consider the risk/benefit of continuing ibrutinib based on the individual subject's underlying condition and the potential risks associated with COVID-19.
- If the subject becomes symptomatic at any point, refer to guidance below for subjects with symptomatic COVID-19 infection.

For subjects who have been diagnosed with COVID-19:

- The investigator should contact the sponsor's responsible medical officer to discuss plans for study treatment and follow-up.
- The investigator should consider the risk/benefit of continuing ibrutinib based on the nature and status of the subject's underlying condition and the potential risks associated with COVID-19.
- As with all infections, the investigator should follow the protocol guidance which is to interrupt therapy for Grade 3 or higher non-hematologic AE (see Section 6.1), and resume once infection has resolved to Grade 1 or baseline (recovery). Given that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a new pathogen, a more cautious approach would be appropriate, with interruption for confirmed cases of SARS-CoV-2 infection of any grade.

On-site Monitoring Visits

In case on-site monitoring visits are not possible, as per institution policies, the sponsor's site managers may contact the investigator to arrange remote monitoring visits. Additional on-site monitoring visits may be needed in the future to catch up on source data verification.

All of the above measures are recommended for consideration on a temporary basis during the COVID-19 pandemic to enable continuity of treatment and to ensure that subject assessments, particularly those assessing relapse and safety, continue as outlined in the protocol without imposing health risk to subjects, their families, and site staff. Every effort should be made to complete all protocol-required assessments. Investigators should use their clinical judgment and risk/benefit assessment in determining if a subject can continue study treatment in the absence of on-site clinic visits. If remote visits are not possible, or if in the investigator's judgment, appropriate safety monitoring is not feasible in a remote setting, the investigator should consider temporarily interrupting study treatment (for a maximum of 28 consecutive days, unless reviewed and approved by the sponsor) or discontinuing study treatment.

INVESTIGATOR AGREEMENT

COVID-19 Appendix
JNJ-54179060 (ibrutinib) Clinical Protocol 54179060CLL3011

INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study intervention, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____
(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____
(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): Donne Bennett Caces, MD PhD

Institution: Janssen Research & Development

Signature: PPD Date: 24Apr2020
(Day Month Year)

Note: If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.