Janssen Research & Development*

Clinical Protocol

Randomized, Double-blind, Placebo-controlled Phase 3 Study of Ibrutinib, a Bruton's Tyrosine Kinase (BTK) Inhibitor, in Combination with Bendamustine and Rituximab (BR) in Subjects With Relapsed or Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

Protocol PCI-32765CLL3001; Phase 3
Amendment INT-7

JNJ-54179060 (ibrutinib)

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This compound is being investigated in Phase 1, Phase 2, and Phase 3 clinical studies.

This study will be conducted under US Food & Drug Administration IND regulations (21 CFR Part 312).

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PROTOCOL AMENDMENTS

Protocol Version	Issue Date
Original Protocol	9 May 2012
Amendment INT-1	5 December 2012
Amendment INT-2	13 September 2013
Amendment INT-3	30 January 2014
Amendment INT-4	13 April 2015
Amendment INT-5	29 April 2016
Amendment INT-6	28 September 2016
Amendment INT-7	21 August 2017

Amendments are listed beginning with the most recent amendment.

Amendment INT-7 (21 August 2017)

This amendment is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union, in that it does not significantly impact the safety or physical/mental integrity of subjects, nor the scientific value of the study.

The overall reason for the amendment: The overall reason for the amendment is to provide an end date for minimal residual disease (MRD) assessment collection (to be discontinued as of 31 July 2017).

Applicable Sections	Description of Changes
Rationale: The study objective to evaluate the rate of MRD-negative remission has been met and sufficient MRD data have been collected to determine change in depth of response over time with a median follow-up of over 3 years.	
Time and Events Schedule – After Interim Analysis; Time and Events Schedule - Crossover to Ibrutinib;	Footnote (h) added to T&E Schedule-After Interim Analysis and Footnote (l) added to T&E Schedule-Crossover to Ibrutinib: The last date for MRD collection is 31 July 2017; no further MRD data will be collected after that date.
9.2.1.3. Bone Marrow Assessment	The following footnote was added to the Section 9.2.1.3 heading: With the implementation of Amendment INT-7, collection of all MRD data is discontinued. The last date for MRD collection is 31 July 2017, which corresponds to approximately 5 years after the first subject entered the study; no further MRD data will be collected after that date.

Amendment INT-6 (28 September 2016)

This amendment is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The overall reason for the amendment: To provide an end date for electronically-collected patient-reported outcome (ePRO) data.

Applicable Section(s)	Description of Change(s)
Rationale: To provide an end date (18 September 2016 [4 years after the first subject entered the study]) for collection of ePRO data since pre-specified study objectives to evaluate subjects' quality of life have been met and sufficient ePRO data have been collected.	

Applicable Section(s)	Description of Change(s)
Synopsis Efficacy Evaluations/Endpoints; Time and Events Schedule-After Interim Analysis: Applies to Subjects Continuing Ibrutinib or Subjects in Follow-up; Time and Events Schedule-Crossover to Ibrutinib; 9.2.1.5 Patient-Reported Outcomes	Following text added to Synopsis: With Amendment INT-6, collection of all ePRO data is discontinued. The last date for ePRO collection is 18 September 2016, which corresponds to 4 years after the first subject entered the study; no further ePRO data will be collected after that date. Footnote (g) added to T&E Schedule-After Interim Analysis and Footnote (k) added to T&E Schedule-Crossover to Ibrutinib: The last date for ePRO collection is 18 September 2016, which corresponds to 4 years after the first subject entered the study; no further ePRO data will be collected after that date. Following text added to Section 9.2.1.5: With the implementation of Amendment INT-6, collection of all ePRO data is discontinued. The last date for ePRO collection is 18 September 2016, which corresponds to 4 years after the first subject entered the study; no further ePRO data will be collected after that date.
Rationale: Inactive website link to examples of CYP3A4/5 inhibitors/inducers removed and replaced with working link.	
8.3 Precautions with Concomitant Medications; Attachment 3	The following link deleted (http://www.pharmacologyweekly.com/content/pages/online-drug-therapy-tables), as well as corresponding reference, and replaced with working link from Attachment 3. Inactive link, as well as corresponding reference, deleted from Attachment 3.

Amendment INT-5 (29 April 2016)

This amendment is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The overall reason for the amendment: To provide clarity surrounding MRD evaluations in subjects with CR, response assessments following Amendment INT-4, and criteria for disease progression for subjects with new onset of lymphocytosis.

Applicable Section(s)	Description of Change(s)
Rationale: To align the MRD evaluations with other ibrutinib CLL studies.	
Time and Events Schedule-After Interim Analysis: Applies to Subjects Continuing Ibrutinib or Subjects in Follow-up; Time and Events Schedule-Crossover to Ibrutinib; 9.2 Efficacy; 9.2.1.3 Bone Marrow Assessment	For subjects with suspected CR, in addition to a bone marrow aspirate sample, a concurrent peripheral blood sample will be sent for MRD analysis.
Rationale: To address questions from investigators.	

Applicable Section(s)	Description of Change(s)
9.2.1.1 Radiographic; Imaging Assessment; 9.2.1.4 Response Categories	Clarified the timing and scope of efficacy evaluations following Amendment INT-4. Clarified how to assess a response at a visit that does not include a radiographic assessment.
Rationale: To clarify when the new onset of lymphocytosis meets the criteria for disease progression and to align the definition with other CLL studies in the ibrutinib program.	
Table 1 Criteria for Response Categories	Text added: "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."
Rationale: The definition for the adverse event of special interest of major hemorrhage has been clarified and intracranial hemorrhage is subsumed within the new definition for major hemorrhage.	
11.7 Safety Analyses; 12.3.3.1 Major Hemorrhage; 12.3.3.2 Intracranial Hemorrhage (section deleted)	Intracranial hemorrhage is no longer mentioned separately from major hemorrhage; rather, it is subsumed within the new definition for major hemorrhage.
Rationale: To align the protocol with the latest safety information on drug-drug interactions of ibrutinib.	
8.3 Precautions with Concomitant Medications	Text regarding use of CYP3A4/5 inhibitors was revised to the following: "If a moderate CYP3A inhibitor must be used, reduce ibrutinib treatment to 140 mg for the duration of the inhibitor use. For subjects who are already on a moderate CYP3A inhibitor concomitantly with ibrutinib without significant toxicity, the investigator may consider the overall risk-benefit to determine if a dose reduction of ibrutinib is appropriate."
Rationale: Minor clarification in the Time and Events Schedule-After Interim Analysis: Applies to Subjects Continuing Ibrutinib or Subjects in Follow-up.	
Time and Events Schedule-After Interim Analysis: Applies to Subjects Continuing Ibrutinib or Subjects in Follow-up	Added window of ±7 days.
Rationale: Minor errors were noted.	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

Amendment INT-4 (13 April 2015)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The overall reason for the amendment: Following positive interim analysis and pursuant to the independent Data Monitoring Committee (DMC) recommendations on 10 March 2015, the study is unblinded and placebo subjects will be offered treatment with ibrutinib. Subjects continuing on ibrutinib will have a reduced schedule of assessments.

Applicable Section(s)	Description of Change(s)
Rationale: To provide access to ibrutinib within this study for subjects who received placebo. IRC-confirmed disease progression is no longer a requirement for crossing over to receive ibrutinib.	
Synopsis Overview of Study Design, Synopsis Dosage and Administration; Time and Events Schedule; 2. Objectives; 3.1 Overview of Study Design; 3.1.1 Treatment With Ibrutinib After Interim Analysis; 4 Subject Selection; 5 Treatment Allocation and Blinding; 9.1.5 Crossover to Ibrutinib Treatment; 9.5 Safety Evaluations; Attachment 10	Access to ibrutinib for subjects on placebo may be provided at the discretion of the investigator at the time the subject has progression or meets IWCLL criteria for treatment. Broader eligibility criteria for crossover to ibrutinib. Reduced schedule of assessments and number of laboratory evaluations.
Rationale: To address the FDA request to follow subjects receiving ibrutinib until the median progression-free survival (PFS) is reached.	
Synopsis Overview of Study Design; 3.1 Overview of Study Design; 17.9.1 Study Completion	End of study definition was revised to change the length of time from last patient in study from 4 years to 5 years so that median PFS can be reached.
Rationale: Studies have been conducted to evaluate the effect of food on the absorption of ibrutinib. Population pharmacokinetics analysis showed that mean systemic exposure (area under the plasma concentration-time curve [AUC]) in 16 subjects with CLL taking ibrutinib in the fed condition was not significantly higher than the mean AUC in the complete pharmacokinetic population instructed to take the drug at least 30 minutes before or 2 hours after a meal. Instructions specific to ibrutinib administration have been revised to remove the restriction of "approximately 30 minutes before eating or approximately 2 hours after a meal".	
6.2 Administration	Deleted text: Each dose of study medication should be taken at least 30 minutes before eating or approximately 2 hours after a meal, at approximately the same time each day.

Applicable Section(s)	Description of Change(s)
Rationale: At the time of Protocol Amendment INT-4, the last dose of BR given to any subject was more than 9 months ago. The study is unblinded for primary analysis and considered completed in regards to evaluation of BR. The study will continue for the purpose of evaluating long-term efficacy and safety of ibrutinib.	
16.2.2 Independent Ethics Committee or Institutional review Board	As of Amendment INT-4, reports of adverse events that are serious, unlisted/unexpected, and associated with bendamustine or rituximab will no longer be provided for reporting to IEC/IRB.
Rationale: To describe the planned PFS and overall survival assessments to be done after the interim analysis.	
11.4.1 Primary Efficacy Endpoint	Text added: After interim analysis, PFS and overall survival will be updated in subsequent analysis.
Rationale: Ibrutinib has been approved for the treatment of mantle cell lymphoma and chronic lymphocytic leukemia since this protocol was first issued.	
1 Introduction	Text regarding the approval status of ibrutinib was revised to include updated information regarding approvals for MCL and CLL.
Rationale: Correction of numeric symbol associated with GFR calculation and broadening eligibility criteria for crossover to ibrutinib.	
9.1.5 Crossover to Ibrutinib Treatment	The criterion for estimated GFR (Cockcroft-Gault) was updated to ≥30 mL/min.

Amendment INT-3 (30 January 2014)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The overall reason for the amendment: To provide access to next-line treatment with ibrutinib within this study for subjects initially assigned to placebo who have independent review committee (IRC)-confirmed disease progression (ie, each subject has met the primary endpoint), at investigator's discretion and with medical monitor approval. The aim is to protect the primary endpoint by mitigating potential early dropout and also to provide an opportunity of access to ibrutinib for subjects who previously received placebo. This crossover is triggered by (a.) the recently released positive interim results of Study PCYC-1112-CA, which demonstrated significant benefit in progression-free survival and overall survival for subjects with relapsed/refractory CLL treated with ibrutinib compared to ofatumumab, and (b.) anticipated increasing access to ibrutinib through commercial, named-patient program or other access programs. Crossover has been discussed and agreed with the DMC for Study PCI-32765CLL3001.

Applicable Section(s)	Description of Change(s)
Rationale: To provide access to ibrutinib within this study for subjects who received placebo and have IRC-confirmed disease progression and meet the IWCLL criteria for requiring subsequent anti-CLL therapy.	
Synopsis; Time and Events Schedule; Time and Events Schedule for Subjects with IRC-confirmed Progression Who are Eligible to Receive Next-line Ibrutinib; 3.1 Overview of Study Design (Figure 2); 3.1.1 Unblinded Next-Line Treatment With Ibrutinib (new section); 4.1 Inclusion Criteria; 5 Treatment Allocation and Blinding; 9.1.5 Next-line Ibrutinib Treatment (new section); 9.2.1.5 Patient-Reported Outcomes; 9.4 Biomarkers; 9.5 Safety Evaluations; Attachment 4	At investigators request, subjects who have IRC-confirmed disease progression and meet the IWCLL criteria for requiring subsequent anti-CLL therapy and other eligibility criteria may be considered for next-line ibrutinib treatment. If upon unblinding by a medical monitor separate from the study team it is determined that the subject was randomized to placebo, the subject will be permitted to cross over to receive ibrutinib 420 mg orally, daily. Open-label next-line treatment with ibrutinib will continue until disease progression, unacceptable toxicity, withdrawal from study, or until the study end, whichever occurs earlier. Text describing eligibility criteria for subjects who crossover from placebo to ibrutinib treatment, as well as a new Time and Events Schedule (Time and Events Schedule for Subjects with IRC-confirmed Progression Who are Eligible to Receive Next-line Ibrutinib) have been added. Operational details for the crossover treatment period have been added. Safety evaluations for the crossover treatment period have been added.
Rationale: Additional new safety information (rashes, and infection) based on studies conducted with ibrutinib has been added.	
Abbreviations; 1.2.2.4 Overview of Clinical Safety	Added language on severe rash, including Stevens-Johnson Syndrome (SJS) and infections.

Applicable Section(s)	Description of Change(s)
Rationale: Clarification to IWCLL criteria for partial response was published in November 2013.	
9.2.1.4 Response Categories (Table 1); References	Note added to Table 1 to align with recently published clarification to IWCLL response criteria. Reference by Hallek et al (2013) providing clarification of IWCLL criteria for a partial response has been added to list of references.
Rationale: On November 13, 2013 the FDA approved ibrutinib for the treatment of adult patients with MCL who have received at least one prior therapy. Therefore, the statement below indicating ibrutinib has not been approved has been deleted.	
1.2 Ibrutinib	The following text has been deleted: "Ibrutinib is an investigational product that has not been approved for marketing in any country." Text regarding the US approval has been added.
Rationale: Safety data, since the time the original protocol was finalized, have been updated. These data included information from the 2013 Investigator's Brochure.	
1.2.2.4 Overview of Clinical Safety	At the time of the original protocol (09 May 2012), safety data for 312 subjects were available. Safety data as of 06 Apr 2013 for the 506 subjects treated with ibrutinib monotherapy and 130 subjects treated with ibrutinib in combination with chemotherapy have been added. The following text has been deleted: Slight corneal dystrophy and opacity were observed in dogs treated at the highest dose (ie, 150 mg/kg/day) in nonclinical toxicology studies. Grade 1 or 2 ocular findings (ie, blurred vision, dry eye, eye pain, visual impairment, and increased lacrimation) have been reported in clinical studies. The events were considered unrelated to ibrutinib treatment.
Rationale: Minor errors were noted.	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

Amendment INT-2 (13 September 2013)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The overall reason for the amendment: The overall reason for the amendment is to update the protocol for consistency with updated safety information in the new Investigator's Brochure (IB; version 7) and to implement a recommendation from the Data Monitoring Committee (DMC).

Applicable Section(s)	Description of Change(s)
Rationale: To clarify the mechanism of action of ibrutinib.	
Synopsis; 1.2 Introduction	Based on current information, the description of the mechanism of action of ibrutinib as a potent, orally-administered, covalent small molecule inhibitor of Bruton's tyrosine kinase (BTK) has been updated in the protocol.

Applicable Section(s)	Description of Change(s)
Rationale: To clarify cycle duration and other scheduling guidance.	
Time & Events Schedule	Added cycle length to footnote "a" as follows: A standard cycle should be no less than 26 days and no more than 30 days. Changed footnote "l" as follows: Must be done within 7 days prior to randomization ~~in order to meet inclusion criteria~~.
4.1 Inclusion Criteria Incl. #7 and #8	Deleted "within 7 days prior to randomization" for hematology and chemistry from entry criteria. Retained it as a mandatory requirement in Time & Events schedule.
9.1.3 Double-blind Treatment Phase and End of Treatment	Added that the End-of-Treatment Visit shall have a 30 day +7-day window to be consistent with the collection of adverse events that occur within 30 days after the last dose of study treatment.
Rationale: To align with the most recent protocol template update (29 March 2013)	
4.2 Exclusion Criteria	Updated note to exclusion criteria that if a subject's health status changes such that he or she no longer meets eligibility criteria, he or she may not participate in the study.
12.3.1 All Adverse Events	Updated that all subjects will be instructed to carry the study card with them for the duration of the study.
13.1 Procedures	Updated that all product quality complaints (PQCs) should be reported to the sponsor within 24 hours.
Rationale: To align with the annual IB update.	
1.2.2.1 Human Pharmacokinetics	Updated the following with final results from Study PCI-32765CLL1002:-Results demonstrated a 24-fold increase in ibrutinib area under the plasma concentration-time curve ($AUC_{0\text{-last}}$) and a 29-fold increase in C_{max} following co-administration with ketoconazole.
1.2.2.3 Treatment-related Lymphocytosis	Updated background information on the potential for observed transient lymphocytosis in some patients treated with ibrutinib.
1.2.2.4 Overview of Clinical Safety	Updated the paragraph describing hemorrhagic events and added paragraph on other malignancies.
12.3.1 All Adverse Events	Added instructions on appropriate reporting interval for all new malignancies.
8.1 Permitted Medications	Added background information describing the risk of leukostasis in subjects treated with ibrutinib and provided supportive care and management guidelines for subjects considered at risk.
11.7 Safety Analyses	Added information on the reporting of adverse events of special interest with ibrutinib, major hemorrhage and intracranial hemorrhage.
Rationale: To provide further clarifications of existing text.	
3.1 Overview of Study Design; Definitions of Terms; Throughout the document	Added text defining the use of the terms study treatment (bendamustine hydrochloride, rituximab, and ibrutinib/placebo) and study drug (ibrutinib/placebo) within this protocol. Clarified that the End-of-Treatment Visit should be scheduled within 30 days of the last dose of study treatment (ie, bendamustine, rituximab, or oral study drug) and not exclusively the study drug. Clarified that the Follow-up Phase will begin once a subject discontinues study ~~medication~~ **treatment**.
8.1 Permitted Medications	Clarified that pre-medication is permitted not only for rituximab but also for bendamustine infusion**s** per the respective package inserts.

Applicable Section(s)	Description of Change(s)
6.3 Dose Modification (Bendamustine)	Modified the following statement: If bendamustine hydrochloride is discontinued for toxicity, then treatment with rituximab may be continued. ~~for up to 6 cycles~~.
6.3 Dose Modification (Study Medication)	Clarified that for Grade 3 thrombocytopenia (platelets <50 x 10^9/L [ie, <50,000/µL]) dose modifications of oral study medication should be done only if this toxicity is accompanied by significant bleeding.
4.2 Exclusion Criteria Excl. #5	Clarified that subjects will be excluded if they were previously treated with a bendamustine-containing regimen who did not achieve a response or who relapsed **and required treatment** within 24 months of treatment with that regimen.
6.3 Dose Modification (Rituximab)	Added that if rituximab is discontinued for toxicity, then treatment with bendamustine hydrochloride may be continued.
6.3 Dose Modification (Study Medication)	Added that if ibrutinib or placebo is discontinued for toxicity, then treatment with bendamustine hydrochloride and rituximab may be continued.
9.1.3 Double-blind Treatment Phase	Clarified that rituximab administration must begin after randomization: Subjects must start rituximab within 72 hours ~~of~~ **after** randomization.
Rationale: Further clarified the requirements regarding Cyclin D 1 or BCL-1 testing for diagnostic purposes.	
4.1 Inclusion Criteria Incl. # 2c	Added a clarification statement explaining that these tests are required only when the diagnosis of CLL/SLL is not otherwise clear.
Rationale: Clarified that subjects who have had their study treatment assignment unblinded due to an emergency may continue study treatment with the approval of the sponsor.	
5 Treatment Allocation and Blinding	Modified wording to: "Subjects who have had their treatment assignment unblinded should continue to return for scheduled evaluations **and with sponsor approval may continue study treatment**."
Rationale: To ensure continuous administration of the oral study medication.	
6.2 Study Drug Administration	Removed the requirement to skip a dose of ibrutinib/placebo when a dose was not taken within the 6-hour window of the scheduled time stipulated in the protocol.
Rationale: For further safety precautions	
Section 6, Dosage and Administration	Provided guidance regarding bendamustine dosing in the event of rituximab-related toxicity (eg, infusion reactions).
Rationale: Bendamustine is a more bone marrow suppressive drug than ibrutinib; however, the hematologic criteria for re-initiating ibrutinib are more stringent than those of bendamustine. The purpose of this change is to eliminate inconsistencies between the hematologic criteria used for re-initiation of ibrutinib and bendamustine	
6.3 Dose Modification (ibrutinib/placebo table)	Aligned the instructions for re-initiation of oral study medication following severe hematologic toxicity with those of bendamustine by adding a footnote to the table.

Applicable Section(s)	Description of Change(s)
Rationale: Levact®/Ribomustin® package insert does not require withholding the drug for mild or moderate hepatic impairment whereas TREANDA® insert recommends discontinuations for mild and moderate hepatic impairment. Some of the sites follow TREANDA package insert, others use Levact/Ribomustin package insert. This change will align the protocol guidance with both package inserts.	
6.3 Dose Modification (Bendamustine hydrochloride)	Clarified the wording regarding administration of bendamustine in the event of elevated transaminases or elevated bilirubin as follows: **Withholding of** bendamustine hydrochloride should be **considered** ~~discontinued~~ in the event of AST or ALT value >2.5 X ULN or total bilirubin value >1.5 X ULN.
Rationale: To implement Data Monitoring Committee recommendation	
8.1 Permitted Medications	Added wording that "Use of anti-microbial prophylaxis (eg, pneumocystis pneumonia prophylaxis with sulfamethoxazole and trimethoprim or equivalent) according to the institution's guidelines is strongly recommended."
Rationale: To clarify that certain medications are prohibited only during the Treatment Phase and not during the Follow-up Phase.	
8.2 Prohibited Medications	Modified wording to "The following medications are prohibited during **the treatment phase of** the study: any chemotherapy (other than BR), anticancer immunotherapy, corticosteroids (at dosages equivalent to prednisone >20 mg/day), experimental therapy, and radiotherapy."
Rationale: To update the guidelines for use of concomitant medication with ibrutinib based on the results of clinical studies.	
8.3 Precautions with Concomitant Medications; Attachment 3	Clarified the concomitant use of ibrutinib with CYP3A4/5 inhibitors/inducers, QT prolonging agents, and antiplatelet agents and anticoagulants during the study; added section on drugs that have their plasma concentrations altered by ibrutinib.
Rationale: Conventional cytogenetics is not commonly used to characterize CLL in countries around the world and therefore, is being removed from the protocol as a mandatory technique.	
Time & Events Schedule, 9.1.2 Screening Phase, 9.2.1.3 Bone Marrow Assessment	Changed conventional cytogenetics (ie, karyotyping) to an optional procedure. Added that, for subjects with SLL, a lymph node biopsy may be used for immunophenotyping, morphology, and FISH testing to confirm the diagnosis.
Rationale: For consistency with other CLL protocols in the program	
9.1.4 Follow-up phase	Added that any data related to the occurrence of other malignancies or transformation to a more aggressive histology (Richter's transformation) during the Follow-up phase needs to be collected.
Rationale: To align the Patient-Reported Outcomes (PRO) collection with the clinical schedules	
9.1.1 Overview; 9.2.1.5 Patient-Reported Outcomes	All visit-specific PRO assessments during a visit should **preferably** be conducted before any tests… The PRO questionnaires will be collected p**referably** at the beginning of the clinic visits prior to any procedures or physician interactions according to the schedule described in the Time and Events Schedule.

Applicable Section(s)	Description of Change(s)
Rationale: To align with Pharmacyclics, Inc. protocols and also with the IRC charter	
Time & Events Schedule; 9.2.1.3 Bone Marrow Assessment	Clarified that after the completion of BR, a bone marrow or aspirate should be collected in the event of a new onset of cytopenia to determine the underlying cause. Added this information to footnote "j" in the Time & Events Schedule.
Rationale: Total bilirubin is composed of direct and indirect; therefore, if total bilirubin is within normal range, then direct bilirubin is not expected to be elevated and is usually not measured in those circumstances.	
9.5. Safety Evaluations (Clinical Laboratory Tests)	Changed direct bilirubin sampling to an optional procedure when total bilirubin is within normal limits.
Rationale: To provide further clarification in line with the latest published guidelines and also to be aligned with the protocols across the ibrutinib program	
9.5. Safety Evaluations (Clinical Laboratory Tests)	Added that monitoring of Hepatitis B polymerase chain reaction (PCR) and liver enzymes and prophylactic antiviral medication should be considered per published guidelines for at least 12 months following the last dose of rituximab.
Rationale: To clarify how body surface area (BSA) calculations are performed by the interactive web response system (IWRS) at each visit.	
9.5 Safety Evaluations (Body Surface Area)	Clarified that the initial BSA is recalculated only if a subject experiences a >10% change in weight in subsequent cycles.
Rationale: To further clarify the hematologic adverse event grading for subjects with advanced CLL/SLL	
12.1.3 Severity Criteria	Modified Table 2 to further align with the IWCLL criteria for evaluation of hematologic toxicity.
Rationale: For completeness	
Attachment 2	Added Ann Arbor staging system for SLL subjects.
Rationale: To allow sufficient amount of peripheral blood to be collected to confirm and characterize the diagnosis of CLL by immunophenotyping and FISH analysis.	
9.1.1 Overview; 16.1 Study Specific Design Considerations; Attachment 4	Increased the volume of peripheral blood sample for diagnosis of CLL in the blood volume table; added a footnote to the table indicating that the blood volume required for CLL diagnosis may vary by country or site, therefore, additional blood may be drawn to be sent to a separate local laboratory; updated the total blood volume estimated to be collected in the first year will normally not exceed 335 mL in the corresponding sections of the text.
Rationale: Minor errors were noted.	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

Amendment INT-1 (5 December 2012)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The overall reason for the amendment: The overall reason for the amendment is to clarify management of study medication with concomitant CYP3A4/5 inhibitors/inducers and warfarin or other anticoagulants, to clarify management of study medication during the perioperative periods, and to incorporate feedback from investigators, health authorities, and the study Steering Committee.

Applicable Section(s)	Description of Change(s)
Rationale: Prohibited equivalent vitamin K antagonists (in addition to warfarin) as a precautionary safety measure.	
4.2. Exclusion Criteria	Modified criterion #13 to exclude subjects requiring anticoagulation with equivalent vitamin K antagonists (eg, phenprocoumon), in addition to warfarin.
Rationale: Updated the guidelines for concomitant use of anticoagulants as a precautionary safety measure.	
6.3. Dose Modification	Removed detailed text on concomitant administration of study medication and anticoagulant treatment and referred to section 8.3.
8.3. Precautions with Concomitant Medications	Updated the text for the management of study medication with anticoagulants during the study, to reflect updated standard language and ensure consistency across ibrutinib protocols. Clarified that the concomitant use of warfarin or equivalent vitamin K antagonists (eg, phenprocoumon) with study medication is prohibited during the study. Removed the need for a PK sample in the case of a bleeding event.
Rationale: Updated the guidelines for concomitant use of CYP-inhibiting/inducing drugs based on the results of clinical pharmacology studies.	
4.2. Exclusion Criteria; Attachment 3	Removed the eligibility restriction for subjects requiring treatment with strong CYP2D6 inhibitors in the exclusion criteria. Removed the list of CYP2D6 inhibitors from Attachment 3.
8.3. Precautions with Concomitant Medications	Updated the text for the management of ibrutinib with CYP3A4/5 inhibitors/inducers during the study, to reflect updated standard language and ensure consistency across ibrutinib protocols.
Rationale: Platelet cutoff is being changed for consistency with the Phase 1b/2 Study PCYC-1108-CA evaluating bendamustine, rituximab, and ibrutinib.	
4.1. Inclusion Criteria; 6.3. Dose Modification	Modified inclusion criterion and requirement for bendamustine reinstatement following hematologic events to platelet count of ≥50 x 10^9/L (ie, ≥50,000/μL) instead of ≥75 x 10^9/L (ie, ≥75,000/μL).
Rationale: For further safety precautions.	
4.3. Prohibitions and Restrictions	Added guidelines for subjects who require surgical intervention while receiving study medication and referred to this section in Section 6.3.
6.3. Dose Modification	Modified dose modification criteria of study medication for Grade 4 neutropenia.
8.1. Permitted Medications	Added statement that the rituximab dose may be split over 2 days during Cycle 1 for subjects with an increased risk of TLS.

Applicable Section(s)	Description of Change(s)
Rationale: To provide further instructions about bone marrow aspirate and biopsy sampling.	
Time & Events Schedule; 9.1.2. Screening Phase; 9.2.1.3. Bone Marrow Assessment; 9.5. Safety Evaluations; Attachment 4	Clarified the timing, methodology, and purpose of the bone marrow biopsy and aspirate (or peripheral blood) samples at screening and during the study. Modified the wording of the cytogenetics row and footnote in the Time & Events schedule for clarity. Included the peripheral blood sample for diagnosis of CLL in the blood volume table in Attachment 4.
Rationale: To provide clarity surrounding MRD evaluations.	
Time & Events Schedule; 9.2.1.3. Bone Marrow Assessment	Further defined the timing and methodology of MRD assessments during the study.
Rationale: To delete unnecessary screening procedures and to increase safety measures at the time of adverse events.	
Time & Events Schedule; Attachment 4	Deleted row for Coombs test in the Time & Events Schedule and the blood volumes table.
9.5. Safety Evaluations	Removed reticulocytes and Coombs from screening requirements. Added that local laboratories may be used for reticulocyte count and Coombs test for adverse events.
Rationale: To eliminate inconsistency between definition of refractory and exclusion criterion #5.	
3.1. Overview of Study Design	Deleted the following statement: Refractory is defined as either failure to achieve at least a PR to therapy or relapse within 12 months of combination CIT or purine analog systemic therapy.
Rationale: To expand evaluations that will be collected during the follow-up phase, consistent with health technology agency advice.	
3.1. Overview of Study Design, Figure 2; 9.1.4. Follow-up Phase	Added that during the follow-up phase, the IWCLL criteria that were met during subsequent therapy will be collected, as well as response to subsequent therapy.
Rationale: To further specify diagnosis to ensure enrolled subjects have CLL (and not MCL).	
4.1. Inclusion Criteria	Expanded CLL/SLL diagnosis criteria to include criterion “c.”
Rationale: For consistency with bendamustine package insert.	
4.1. Inclusion Criteria	The length of time required for practicing highly effective birth control methods after the last dose of bendamustine was made consistent for men and women (ie, 6 months) in criterion #9.
6.3. Dose Modification	Clarified existing dose modification criteria for bendamustine, and added criteria for bendamustine discontinuation due to hepatotoxicity.

Applicable Section(s)	Description of Change(s)
Rationale: For consistency with the package insert for rituximab.	
6.3. Dose Modification	Modified the statement that describes when the rituximab dose should be held.
Rationale: To align with the IRC charter.	
9.2.1.4. Response Categories and Table 1	Expanded on lymph nodes, liver, and spleen criteria for disease response (PR and PD), and expanded the definition of PD.
Rationale: Validation of the CLL-16 has not been completed by EORTC. The scoring and measurement properties of the CLL-16 may be evaluated as part of this study.	
9.2.1.5. Patient-Report Outcomes	Added statements explaining that alternate scoring approaches for the CLL-16 may be considered and that psychometric validation of the CLL-16 may be conducted using blinded treatment group data prior to database lock.
Rationale: To describe what multiplicity adjustment will be done for secondary PRO endpoints.	
11.4.3. Analysis Methods	Clarified that details of multiplicity adjustment for secondary PRO endpoints to control alpha will be specified in the SAP.
Rationale: To prevent the need for future protocol amendments in the event of changes in capsule size or color.	
14.1. Physical Description of Study Drugs	Removed reference to “gray” color and “size 0” of capsules.
Rationale: Updated attachment for compliance with privacy requirements.	
Attachments	In Attachment 6, subject’s initials and date of birth have been deleted to protect subject’s identity.
Rationale: For consistency with the CRF and clinical practice in case of adverse events.	
9.5. Safety Evaluations	Added that additional laboratory parameters may be obtained at unscheduled visits.
Rationale: To aid with clinical trial registry procedures.	
Title page; synopsis	Added the Universal Trial Number (UTN).
Rationale: For consistency with other ibrutinib protocols.	
1.2.2.1. Human Pharmacokinetics	Added paragraph regarding preliminary results from Study PCI-32765CLL1002.
1.2.2.4. Overview of Clinical Safety	Provided additional detail in the paragraph describing hemorrhagic AEs. Added text regarding mitigation of bleeding risk. Deleted paragraph regarding atrial fibrillation.
4.2. Exclusion Criteria	Moved exclusion criterion for subjects requiring treatment with CYP3A4/5 inhibitors to a separate criterion from the exclusion criterion for subjects requiring anticoagulation with warfarin or equivalent vitamin K antagonists.
6.2. Study Drug Administration	Added statement to clarify the timing of study medication dosing on the days of PK sampling.
6.3. Dose Modification	Clarified that study medication may be held for a maximum of 28 consecutive days, unless reviewed and approved by the sponsor.

Applicable Section(s)	Description of Change(s)
8.2. Prohibited Medications	Clarified that short courses (<14 days) of corticosteroids for non-cancer related medical reasons are permitted at doses not to exceed 100 mg/day of prednisone or equivalent.
8.3. Precautions with Concomitant Medications	Updated the guidelines for use of ibrutinib and QT prolonging agents.
9.5. Safety Evaluations	Added ocular-related symptoms.
Attachment 3	Updated the list of CYP3A4/5 inhibitors, included the appropriate website, and added a statement that the website should be checked for the latest information.
Rationale: Provided further clarification of existing text.	
Time & Events Schedule	Moved "(within 72 hours of randomization)" to the row for rituximab 375 mg/m^2.
3.1. Overview of Study Design	Added more detail for stratification factors by further defining failure to respond and separate lines of therapy.
3.1. Overview of Study Design; 9.5. Safety Evaluations	Deleted "all" when referring to CBC tests are performed at the central laboratory.
4.1. Inclusion Criteria	Added "or SLL" to inclusion criterion #5.
4.2. Exclusion Criteria	Clarified that subjects with active infection with Hepatitis C will be excluded.
7. Treatment Compliance; 14.4. Preparation, Handling, and Storage; 15. Study-Specific Materials	Corrected the name of the pharmacy manual to "Site Investigational Product Procedures."
8.1. Permitted Medications	Added that neutrophil growth factors are permitted per the ASCO guidelines **or according to the institution's guidelines.**
9.1.3. Treatment Phase	Provided additional details regarding the timing of laboratory values and the requirements for meeting eligibility criteria.
9.2. Efficacy Evaluations	Clarified text in MRD bullet that evidence of CR is by clinical parameters (not all response parameters)
9.2.1.1. Radiographic Imaging Assessments	Added additional details regarding imaging assessments.
9.2.1.4. Response Categories; Reference Section	Added reference to IWCLL e-letter by Hallek.
9.2.1.2. Definition of Measureable and Assessable Disease	Added that subjects must have 1 measurable lymph node >1.5 cm to be eligible. Made minor editorial changes in second paragraph regarding additional lesions.
9.4. Biomarkers	Made minor editorial changes for clarity.
15. Study-Specific Materials	Updated the list of supplies provided to investigators.

Applicable Section(s)	Description of Change(s)
Rationale: To correct typographical errors.	
3.1. Overview of Study Design, Figure 2; 9.1.3. Double-Blind Treatment Phase	Clarified that rituximab (and not the study medication) is to be administered within 72 hours of randomization.
9.1.2. Screening Phase	Changed last sentence to "Results will be collected in the CRF and subjects with **≥20%** of cells with del (17p) will not be eligible to participate in the study."
Rationale: For consistency with latest company protocol template.	
10.3 Withdrawal From the Study	Paragraph added on withdrawal from the use of samples in future research.
12.1.1. Adverse Event Definitions and Classifications	Added text regarding EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use.
12.3.1. Adverse Events	Removed subject's date of birth from the study card information. Added text about reporting unlisted and associated SAEs to the head of the investigational institute where required.
16.2.5. Long-Term Retention of Samples for Additional Future Research	Added section.
17.11. Use of Information and Publication	Clarified when the company and the investigator are permitted to publish data from the study.
Rationale: Minor errors were noted	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

SYNOPSIS

Randomized, Double-blind, Placebo-controlled Phase 3 Study of Ibrutinib, a Bruton's Tyrosine Kinase (BTK) Inhibitor, in Combination with Bendamustine and Rituximab (BR) in Subjects With Relapsed or Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

EudraCT NUMBER: 2012-000600-15

UTN NUMBER: U1111-1135-3745

Chronic lymphocytic leukemia (CLL) is incurable except for the minority of patients who have successful stem cell transplantation. Ibrutinib (PCI-32765; JNJ-54179060) is a first-in-class potent, orally-administered, covalently binding small molecule inhibitor of Bruton's tyrosine kinase (BTK). As a single agent in previously-treated patients with CLL, an overall response rate (ORR) of 67% was observed.

OBJECTIVES AND HYPOTHESIS

Primary Objective

The primary objective is to determine whether the addition of ibrutinib to BR significantly improves progression-free survival (PFS) compared with BR in subjects with relapsed or refractory CLL/SLL.

Secondary Objectives

The secondary objectives are to evaluate the following: safety; ORR; overall survival (OS); rate of minimal residual disease (MRD)-negative remissions; improvement in hematologic parameters (hemoglobin, neutrophil count, platelet count); improvement in disease-related symptoms (fatigue, night sweats, weight loss, fever, and abdominal discomfort due to splenomegaly); and patient-reported symptoms, functional status, and well-being as measured by European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ) C30, EORTC QLQ CLL 16, EQ-5D-5L, and Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue Scale. Other secondary objectives are to characterize the PK of ibrutinib and explore its potential effect on bendamustine and rituximab PK, the potential relationships between ibrutinib metrics of exposure with relevant clinical or biomarker information, and to examine biomarkers related to BCR and compensatory signaling pathways and explore their association with resistance to ibrutinib treatment.

Hypothesis

The primary hypothesis of this study is that the addition of ibrutinib to BR compared with BR alone will significantly improve PFS in subjects with relapsed or refractory CLL/SLL.

OVERVIEW OF STUDY DESIGN

This is a randomized (1:1), double-blind, placebo-controlled, multicenter, Phase 3 study of approximately 580 subjects to determine the benefits and risks of combining ibrutinib and BR in subjects with relapsed or refractory CLL/SLL following at least 1 line of prior systemic therapy. Randomization will be stratified by whether refractory to purine analog therapy (yes or no) and number of prior lines of therapy (1 or >1). All subjects will receive BR as the background therapy plus either ibrutinib or placebo for a maximum of 6 cycles, after which treatment with ibrutinib or placebo will continue until disease progression or unacceptable toxicity. The study will include a Screening Phase, a Treatment Phase, and a Follow-up Phase. Study end is defined as when either 80% of the subjects have died or 5 years after the last subject is randomized into the study, whichever occurs first.

Following the positive outcome of an interim analysis and pursuant to the independent Data Monitoring Committee (DMC) recommendations on 10 March 2015, the study is unblinded. Subjects in the placebo arm will be offered access to ibrutinib at the discretion of the investigator, at determination of disease progression or when the subject meets IWCLL criteria for treatment, as outlined in Section 9.1.5. Such subjects will be treated and assessed according to a separate Time & Events schedule.

SUBJECT SELECTION

Key eligibility criteria include the following: subjects who are ≥18 years of age; have relapsed or refractory CLL or SLL following at least 1 prior line of systemic therapy; have active disease status per the International Workshop on Chronic Lymphocytic Leukemia (IWCLL) criteria with measurable nodal disease by computed tomography (CT); and have an Eastern Cooperative Oncology Group (ECOG) Performance Status score of 0 or 1.

DOSAGE AND ADMINISTRATION

Bendamustine hydrochloride 70 mg/m^2 will be administered via IV infusion over 30 minutes on Cycle 1, Days 2 and 3, and on Cycles 2-6, Days 1 and 2 for up to 6 cycles. Rituximab will be administered at a dose of 375 mg/m^2 on Cycle 1, Day 1, and 500 mg/m^2 in Cycles 2-6, Day 1. A cycle will be defined as 28 days, with the exception of Cycle 1, which will be 29 days to allow for rituximab dosing prior to bendamustine and study medication. Subjects randomized to Treatment Arm A will receive placebo (3 capsules) administered orally once daily continuously. Subjects randomized to Treatment Arm B will receive ibrutinib 420 mg (3 x 140-mg capsules) administered orally once daily continuously. Treatment with study medication (placebo or ibrutinib) will continue from Cycle 1 until disease progression or unacceptable toxicity.

As of Amendment INT-4, access to ibrutinib for subjects on Treatment Arm A (placebo) may be provided at determination of disease progression or when subject meets IWCLL criteria for treatment.

EFFICACY EVALUATIONS/ENDPOINTS

Efficacy evaluations will include CT scans, laboratory testing, focused physical examinations, bone marrow biopsy and aspirate, and assessment of PROs.[a] Subjects will have disease evaluations every 12 weeks until disease progression.

PHARMACOKINETIC EVALUATIONS

In both treatment arms, sparse samples for the development of a population-based pharmacokinetic (PK) approach will be collected from all subjects and evaluated for ibrutinib and potentially for PCI-45227. In addition, for a subset of subjects at selected sites, sparse sampling will be performed in both treatment arms to explore a potential effect of ibrutinib on the PK of bendamustine and rituximab.

BIOMARKER EVALUATIONS

Blood samples will be collected and analyzed to better understand the mechanism of action of ibrutinib with an aim to develop predictors of resistance.

SAFETY EVALUATIONS

Safety will be assessed by adverse events (AEs), physical examinations, laboratory tests, and concomitant medication usage. Specific timing is provided in the Time and Events Schedule.

[a] With Amendment INT-6, collection of all ePRO data is discontinued. The last date for ePRO collection is 18 September 2016, which corresponds to 4 years after the first subject entered the study; no further ePRO data will be collected after that date.

STATISTICAL METHODS

The primary efficacy endpoint of PFS will be determined by an Independent Review Committee (IRC). The study is designed to detect a hazard ratio of 0.7 for the ibrutinib + BR group relative to placebo + BR group (corresponding to an improvement of 43% in median PFS, eg, from 15 months to 21.5 months) with 90% power at a 1-sided significance level of 0.025, using a group sequential testing design. Two analyses are planned: an interim analysis using an O'Brien & Fleming boundary after approximately 171 (50%) PFS events (progressive disease [PD] or death) have occurred, and a final analysis after 342 PFS events have occurred. An independent Data Monitoring Committee (DMC) will review safety data periodically and data from the interim analysis.

TIME AND EVENTS SCHEDULE

NOTE: As of Amendment INT-4: After the interim analysis, subjects will no longer follow this Time and Events Schedule. Subjects will be treated and assessed according to separate T&E Schedules, following this table.

	Screening (within 30 days prior to random-ization)	Treatment Phase (1 Cycle = 28 days)[a]												Post-Treatment Follow-up Phase	
		Cycle 1[a] Day					Cycle 2-6 Day			Cycle 7-12 Day	Cycle 13, 16, etc. (every 3 cycles)	Disease Evaluations Every 12 weeks (±7 days) (Starting on C1, D1)	End of Treatment Visit	Prior to Disease Progression (Every 12 weeks ±7 days)	Following Disease Progression (Every 16 weeks)
		1	2	3	8	15	1	2	15	1	Day 1				
Drug Administration															
Rituximab 375 mg/m^2 (within 72 hours of randomization)		X													
Rituximab 500 mg/m^2							X								
Bendamustine hydrochloride 70 mg/m^2			X	X			X	X							
Study medication (ibrutinib 420 mg or matching placebo)			<----------Continuous---------->												
Dispense study medication and check drug accountability			X				X			X	X				
Ongoing Subject Review															
Concomitant medication[b]	X	<----------Continuous---------->													
Adverse events[b]	X	<----------Continuous---------->													
Procedures															
Informed consent	X														
Medical and disease history	X														
Height, vital signs, and ECOG Performance Status Score	X														
Body surface area (BSA)		X													
Electrocardiogram[c]	X		X					X							
Weight	X	X					X								
Disease-related symptoms and physical examination[d]	X	X				X	X			X		X	X	X	
Patient-reported outcomes (EORTC QLQ-C30 and EQ-5D-5L questionnaires)		X					X[e]			X[e]	X		X	X	X[f]

	Screening (within 30 days prior to random-ization)	Treatment Phase (1 Cycle = 28 days)[a]												Post-Treatment Follow-up Phase	
		Cycle 1[a] Day					Cycle 2-6 Day			Cycle 7-12 Day	Cycle 13, 16, etc. (every 3 cycles)	Disease Evaluations Every 12 weeks (±7 days) (Starting on C1, D1)	End of Treatment Visit	Prior to Disease Progression (Every 12 weeks ±7 days)	Following Disease Progression (Every 16 weeks)
		1	2	3	8	15	1	2	15	1	Day 1				
Patient-reported outcomes (EORTC QLQ-CLL 16 and FACIT-Fatigue Scale questionnaires)		X					X[g]			X[g]	X		X	X	
Disease Evaluations															
CT neck, chest, abdomen, and pelvis[h]	X											X[h]	X	X[h]	
Bone marrow aspirate and biopsy	X[i]											(X)[j]		X[j]	
Minimal residual disease												X[j]		X[j]	
Survival status and subsequent antineoplastic therapies														X	X
Laboratory Assessments[k]															
Complete blood count	X[l]	X	X		X	X	X		X	X	X	X	X	X	
Serum chemistry	X[l]	X	X		X	X	X			X	X		X		
Hepatitis serologies	X														
Urine or serum pregnancy test	X														
aPTT, INR	X														
Serum immunoglobulin and β_2 microglobulin	X											X	X	X	
Cytogenetics (karyotyping and FISH)[m]	X														
Biomarker blood samples[n]		X[n]				X							X		
PK sample (study medication)			X[o]					X[o]							
PK sample (bendamustine)[p]			X[q]					X[q]							
PK sample (rituximab)[p]		X[r]				X[r]	X[r]			X[r]					

[a] For Cycle 1 only, the duration will be 29 days to allow for rituximab dosing prior to bendamustine and study medication. A standard cycle should be no less than 26 days or more than 30 days.

[b] Adverse events and concomitant medications should be recorded from the time of written informed consent up until 30 days after the last dose of study treatment

[c] To be conducted for all subjects at screening. For a subset of subjects at selected sites, additional ECGs will be performed on Day 2 of Cycles 1 and 2 prior to study medication administration, immediately before the 2-hr PK sample for study medication, and immediately before the 4-hr PK sample for study treatment.

[d] The screening physical examination must be a full examination. Follow-up examinations must document presence or absence, or increase or decrease or no change of hepatomegaly, splenomegaly, and lymphadenopathy. Subjects should be questioned regarding changes in ocular status and referred to an ophthalmologist for any Grade ≥2 symptoms.

[e] During Cycles 1-12, the EORTC QLQ-C30 and EQ-5D-5L questionnaires will be performed at the beginning of Cycles 1, 3, 5, 7, and 10.

[f] For the first 3 follow-up assessments, the EQ-5D-5L questionnaire only will be completed by the subject, including subjects who receive next-line ibrutinib therapy. Data will be collected in person (preferred) or via telephone with the subject.
[g] During Cycles 1-12, the EORTC QLQ-CLL 16 and FACIT-Fatigue Scale questionnaires will be performed at the beginning of Cycles 1, 2, 4, 6, 8, and 10.
[h] To be performed every 12 weeks for the first 2 years and then every 6 months until disease progression or death.
[i] A unilateral bone marrow biopsy and bone marrow aspirate or peripheral blood sample must be obtained during screening or up to 90 days before randomization for evaluations described in Section 9.2.1.3.
[j] For subjects with suspected CR, a confirmatory bone marrow aspirate and biopsy must be obtained and an MRD evaluation of bone marrow aspirate must be performed. This should occur no earlier than 2 months following the completion of BR. Subsequent MRD evaluations (peripheral blood) in subjects with CR will occur every 12 weeks with disease evaluations. For subjects with suspected PD based on new onset of cytopenia after the completion of BR, a bone marrow aspirate or biopsy should be performed to determine the underlying cause.
[k] Additional details regarding laboratory testing will be included in the Laboratory Manual.
[l] Must be done within 7 days prior to randomization.
[m] This should be performed on a peripheral blood sample or a bone marrow aspirate. Conventional karyotype evaluations are optional; FISH is required. For subjects with SLL, a lymph node biopsy may be used for immunophenotyping, morphology, and FISH testing to confirm the diagnosis.
[n] Blood samples for biomarker analysis will be collected predose at Day 1 and Day 15 of Cycle 1 and at the end of treatment or at disease progression.
[o] To be obtained at Day 2 of Cycles 1 and 2, at predose, and at 1 hr (window 45-75 min), 2 hrs (window 1.5-2.5 hrs), and 4 hrs (window 3.5-6 hrs) following dosing of study medication.
[p] To be obtained only for a subset of subjects at selected sites. For subjects at the selected sites, participation is mandatory.
[q] To be obtained at Day 2 of Cycles 1 and 2, prior to the start of bendamustine infusion, immediately prior to the end of bendamustine infusion, and at 1 hr (window 45-75 min), 2 hrs (window 1.5-2.5 hrs), and 4 hrs (window 3.5-6 hrs) following dosing of oral study medication administration.
[r] To be obtained at Days 1 and 15 of Cycle 1, Day 1 of Cycles 2-6 prior to starting rituximab infusion, and on Day 1 of Cycles 7-9.

TIME AND EVENTS SCHEDULE — AFTER INTERIM ANALYSIS: APPLIES TO SUBJECTS CONTINUING IBRUTINIB OR SUBJECTS IN FOLLOW-UP

	Treatment Phase	Post-Treatment Follow-up Phase		
	Disease Evaluations Every 12 weeks (±7 days)	**End of Treatment Visit**	**Prior to Disease Progression (Every 12 weeks ±7 days)**	**Following Disease Progression (Every 16 weeks ±7 days)**
Drug Administration				
Ibrutinib 420 mg	<----------Continuous---------->	X[a]		
Dispense ibrutinib and check drug accountability	X			
Ongoing Subject Review				
Concomitant medication	<----------Continuous---------->			
Adverse events	<----------Continuous---------->			
Procedures				
Patient-reported outcomes (EORTC QLQ-C30, EQ-5D-5L, EORTC QLQ-CLL 16 and FACIT-Fatigue Scale questionnaires)[g]	X	X	X	X[b]
Disease Evaluations				
Physical Examination and Disease-related symptoms	X	X	X	
CT neck, chest, abdomen, and pelvis	X[c]		X[d]	
Bone marrow aspirate and biopsy	X[e]			
Minimal residual disease[e,f,h]	X			
Survival status and subsequent antineoplastic therapies			X	X
Laboratory Assessments				
Complete blood count (local labs only)	X	X	X	
Serum chemistry	X			
Biomarker blood samples		X		

[a] Subjects who were on placebo will have an EOT visit. If they do not require immediate treatment, they will continue in follow up until investigator-determined PD.
[b] For the first 3 follow-up assessments, only the EQ-5D-5L questionnaire will be completed by subjects.
[c] To be performed every 24 weeks until disease progression in subjects treated with ibrutinib. No IRC assessments will be required.

[d] Subjects who were previously on ibrutinib who are in Pre-PD follow-up phase will have CT scan performed every 24 weeks until disease progression. Subjects who were previously on placebo who are in Pre-PD follow-up phase will have CT scan performed as per standard of care.

[e] For subjects with suspected CR only, a confirmatory bone marrow aspirate and biopsy must be obtained. A concurrent MRD evaluation of bone marrow aspirate and peripheral blood sample should be performed.

[f] Peripheral blood MRD assessment for all responding subjects

[g] The last date for ePRO collection is 18 September 2016, which corresponds to 4 years after the first subject entered the study; no further ePRO data will be collected after that date.

[h] The last date for MRD collection is 31 July 2017; no further MRD data will be collected after that date.

TIME AND EVENTS SCHEDULE — CROSSOVER TO IBRUTINIB

		Treatment Phase			Follow-up Phase
	Assessment of Eligibility for Ibrutinib Therapy	**Day 1 and every 4 weeks until week 12**	**Every 12 weeks** (±7 days) from week 12 **until PD**	**End-of-Treatment Visit**	**Follow-up (every 16 weeks** ±7 days**)**
Procedures					
Confirmed disease progression or meets IWCLL criteria for treatment[a]	X				
Medical monitor review	X				
Medical history[b]	X				
Informed consent	X				
Drug Administration					
Ibrutinib 420 mg		<----------Continuous---------->			
Dispense ibrutinib and check drug accountability		X	X		
Ongoing Subject Review					
Concomitant medication[c]	<----------Continuous---------->				
Adverse events[c]	<----------Continuous---------->				
Laboratory Assessments					
Complete blood count (local labs only)	X	X[e]	X	X	
Serum chemistry[d]	X				
Biomarkers			X[f]		
Disease Evaluations					
Investigator assessment of response			X[g]		
Minimal residual disease[h,i,l]			X		
Survival status and subsequent antineoplastic therapies					X
Patient-reported outcomes (EQ-5D-5L)[k]		X[j]			

[a] For Amendment INT-3: IRC-confirmed PD; for Amendment INT-4, investigator determined PD.
[b] Only required if crossover occurs >30 days after last dose of blinded study treatment.
[c] All AEs and concomitant medications from the time a signed and dated informed consent form for crossover is obtained until 30 days following the last dose of study drug will be reported.
[d] See Section 9.5 for parameters to be collected.
[e] Additional CBC to be taken at Week 2.
[f] Blood samples for biomarkers will be collected at Week 12 Day 1 and at disease progression.
[g] Investigator assessment of response to be performed every 12 weeks for the first year, and then every 24 weeks thereafter until disease progression. Evaluations are to be performed per standard of care.
[h] For subjects with suspected CR only, a confirmatory bone marrow aspirate and biopsy should be obtained. A concurrent MRD evaluation of bone marrow aspirate and peripheral blood sample should be performed.
[i] Peripheral blood MRD assessment for all responding subjects.
[j] This also applies to subjects with PD who crossover to receive ibrutinib therapy. They will still be required to complete 3 post-PD follow-up EQ-5D-5L assessments every 16 weeks.
[k] The last date for ePRO collection is 18 September 2016, which corresponds to 4 years after the first subject entered the study; no further ePRO data will be collected after that date.

[1] The last date for MRD collection is 31 July 2017; no further MRD data will be collected after that date.

ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviations

AE	adverse event
AIHA	autoimmune hemolytic anemia
ALC	absolute lymphocyte counts
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ANOVA	analysis of variance
aPTT	activated partial thromboplastin time
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
$AUC_{0\text{-last}}$	area under the curve from time 0 to the last observation
β-hCG	beta-human chorionic gonadotropin
BCR	B cell receptor
BR	bendamustine and rituximab
BSA	body surface area
BTK	Bruton's tyrosine kinase
CBC	complete blood count
CI	confidence interval
CIT	chemoimmunotherapy
CLL	chronic lymphocytic leukemia
CNS	central nervous system
CR	complete response
CRF	case report form
CRi	complete response with incomplete marrow recovery
CT	computed tomography
CTCAE	common terminology criteria for adverse events
CYP	cytochrome P450
DLT	dose-limiting toxicity
DMC	Data Monitoring Committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organization for Research and Treatment of Cancer
ESMO	European Society for Medical Oncology
FACIT	Functional Assessment of Chronic Illness Therapy
FACS	fluorescence activated cell sorting
FCR	fludarabine, cyclophosphamide, and rituximab
FISH	fluorescent in situ hybridization
GEP	gene expression profile
GFR	glomerular filtration rate
HIV	human immunodeficiency virus
ICF	informed consent form
IEC	independent ethics committee
IgVH	immunoglobulin variable heavy gene
IL	interleukin
INR	international normalized ratio
IRB	institutional review board
IRC	independent review committee
ITP	autoimmune thrombocytopenia
ITT	intent to treat
IV	intravenous(ly)
IWCLL	International Workshop on Chronic Lymphocytic Leukemia
IWRS	interactive web response system
JRD	Janssen Research & Development, LLC
LDH	lactic acid dehydrogenase

LDT	lymphocyte doubling time
MedDRA	Medical Dictionary for Regulatory Activities
MRD	minimal residual disease
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NHL	Non-Hodgkin's lymphoma
NONMEM	nonlinear mixed-effects modeling
nPR	nodular partial response
ORR	overall response rate
OS	overall survival
PCR	polymerase chain reaction
PCYC	Pharmacyclics, Inc.
PD	progressive disease
PFS	progression-free survival
P-gp	p-glycoprotein
PK	pharmacokinetic(s)
PLL	prolymphocytic leukemia
PR	partial response
PRO	patient-reported outcomes
QLQ	quality of life questionnaire
RT	Richter's transformation
SAE	serious adverse event
SJS	Stevens-Johnson Syndrome
SLL	small lymphocytic lymphoma
SMA	somatic mutation analysis
TLS	tumor lysis syndrome
ULN	upper limit of normal
USPI	United States Package Insert
UTI	urinary tract infection
WBC	white blood cell
WHO	World Health Organization

Definitions of Terms

Study medication or study drug	Ibrutinib/placebo
Study treatment	Bendamustine hydrochloride, rituximab, and ibrutinib/placebo

1. INTRODUCTION

1.1. Chronic Lymphocytic Leukemia

Chronic lymphocytic leukemia (CLL) is the most common form of leukemia in adults in the developed world. It is characterized by an accumulation of monoclonal mature B cells (CD5+CD23+) in the blood, bone marrow, and secondary lymph organs. These cells are constantly being stimulated by their B-cell receptors (BCRs) as well as their interaction with their microenvironment.[8] According to the World Health Organization (WHO), small lymphocytic lymphoma (SLL), a disease which presents with similar pathological findings but without the lymphocytosis, is considered to be a manifestation of the same underlying disorder as CLL.[4]

Once diagnosed, patients may have a variable course, some not requiring treatment for decades and others requiring more urgent treatment, particularly those with clinically symptomatic disease.[20] According to the International Workshop on Chronic Lymphocytic Leukemia (IWCLL) guidelines, the following features are indications for therapy: progressive marrow failure (manifested by anemia or thrombocytopenia), massive or progressive splenomegaly (at least 6 cm or greater), massive lymph nodes (at least 10 cm in the longest diameter), progressive lymphocytosis with a rapid lymphocyte doubling time (LDT) occurring in less than 6 months, worsening autoimmune cytopenias resistant to corticosteroids or other standard treatment, and constitutional symptoms.[22]

Historically, the main frontline treatment for CLL was chlorambucil. Over the past 2 decades, however, new agents and combinations of chemotherapy have been shown to be superior to chlorambucil. Fludarabine and bendamustine were shown to have improved efficacy compared with chlorambucil in randomized studies.[7,26,39] The addition of cyclophosphamide to fludarabine further improved response rates and progression-free survival (PFS) compared with fludarabine alone.[11,16,17,31] The addition of rituximab to fludarabine and cyclophosphamide (FCR) in the frontline setting resulted in significant improvement in PFS and overall survival (OS) compared with fludarabine and cyclophosphamide alone.[21]

A recent Phase 2 study evaluated the combination of bendamustine and rituximab (BR) in patients with relapsed or refractory disease. The median number of prior therapies for CLL was 2 (range 1 to 5). The complete response (CR) rate was 9% and overall response rate (ORR) was 59%. Median PFS was 15 months and median OS was 34 months.[15] However, in the high-risk group of subjects with del (17p), the response was poor, with only 1 (7.1%) of 14 subjects responding with a CR. The median PFS for all 14 subjects was 6.8 months.

1.2. Ibrutinib

Ibrutinib (PCI-32765; JNJ-54179060) is a first-in-class potent, orally-administered, covalently-binding small molecule inhibitor of Bruton's tyrosine kinase (BTK) currently under development for the treatment of B-cell malignancies. Ibrutinib is being co-developed by Pharmacyclics, Inc. and Janssen Research & Development, LLC (JRD). 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.

The investigational drug product is an oral formulation in a hard gelatin capsule form containing micronized ibrutinib. The initial approval of ibrutinib by the United States (US) FDA for the treatment of adult patients with MCL who have received at least one prior therapy was received on 13 November 2013. This indication is based on overall response rate. An improvement in survival or disease-related symptoms has not been established. Subsequently it received approval in the US for the treatment of patients with CLL who have received at least one prior therapy, and for the treatment of CLL patients with 17p deletion. It is also approved in the EU for the treatment of adult patients with CLL who have received at least one prior therapy, or in first line in the presence of 17p deletion or TP53 mutation in patients unsuitable for chemo-immunotherapy. Approvals have also been obtained in a number of other countries worldwide. For the most comprehensive nonclinical and clinical information regarding the efficacy and safety of ibrutinib, refer to the latest version of the Investigator's Brochure.

1.2.1. Nonclinical Studies

The generation and maintenance of normal and malignant B cells is controlled by biochemical signals transmitted by the BCR. Bruton's tyrosine kinase is an enzyme required for BCR signaling. Selective BTK inhibition is a novel approach to target diseases driven by BCR activation, such as CLL/SLL.

In vitro studies have shown that ibrutinib binds covalently to a cysteine residue 481 in the BTK active site, leading to potent and irreversible inhibition of BTK enzymatic activity. In cellular signal transduction assays with a B-cell lymphoma cell line, ibrutinib inhibited autophosphorylation of BTK, and phosphorylation of further downstream kinases.

1.2.2. Clinical Studies

1.2.2.1. Human Pharmacokinetics

Extensive pharmacokinetic (PK) sampling has been performed on approximately 186 subjects across 4 studies (Studies PCYC-04753, PCYC-1102-CA, PCYC-1104-CA, and PCYC-1109-CA). Results show that plasma concentrations of ibrutinib generally increased with increasing dosages from 1.25 to 12.5 mg/kg/day. An increase in ibrutinib AUC was approximately proportional to dose. The coefficient of variation for the AUC ranged from 60% to 107% across all studies. The mean apparent terminal half-life of ibrutinib ranged from 4.3 to 8.9 hours, with median T_{max} of 2 hours. There was no apparent accumulation of ibrutinib exposure after repeated daily dosing.

In Study PCYC-1102-CA, ibrutinib was administered as a fixed dosage of 420 mg/day to subjects with relapsed/refractory CLL/SLL. Approximately 95% of subjects had steady-state ibrutinib AUC values ≥160 ng·h/mL, indicating that the 420-mg/day dose is adequate to achieve exposures yielding full BTK active-site occupancy.

Study PCI-32765CLL1002 was an open-label drug-drug interaction study of 18 men, in which ibrutinib was administered alone at a 120-mg dose or in combination with ketoconazole at a 40-mg dose. Results demonstrated a 24-fold increase in ibrutinib area under the plasma concentration-time curve ($AUC_{0\text{-last}}$) and a 29-fold increase in Cmax following co-administration with ketoconazole. Terminal half-life was not increased.

Ibrutinib single-dose administration was well tolerated. No drug-related adverse events were reported. No Grade 3 or 4 toxicities or serious adverse events were reported.

1.2.2.2. Clinical Efficacy Studies in Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma

As of the end of 2011, more than 300 patients with various B-cell malignancies have received ibrutinib across 7 clinical studies, 4 of which included patients with CLL/SLL. Patients with CLL or SLL have received single-agent ibrutinib across 2 clinical studies: Study PCYC-04753, a Phase 1 dose-finding study in patients with recurrent B-cell lymphoma, and Study PCYC-1102-CA, a Phase 1b/2 study in patients with CLL/SLL. Two additional Phase 1b/2 studies are ongoing to evaluate the safety and efficacy of ibrutinib in combination with chemoimmunotherapy (CIT) or CD20 monoclonal antibody therapy in patients with relapsed or refractory CLL/SLL, specifically with BR or FCR in Study PCYC-1108-CA, and with ofatumumab in Study PCYC-1109-CA.

1.2.2.2.1. Study PCYC-04753

This was a Phase 1, multicenter, dose-escalation study of ibrutinib in subjects with surface immunoglobulin positive B-cell Non-Hodgkin's Lymphoma (NHL). Subjects were observed for dose-limiting toxicities (DLTs) and other adverse events (AEs) as well as for laboratory and physical examination changes. Fifty subjects were evaluable for efficacy. The ORR was 60%, with 7 CRs and 23 PRs. Safety data are available for 65 subjects. The most common AEs were diarrhea (41.5%), fatigue (38.5%), cough (27.7%), nausea (26.2%), headache (21.5%), and pyrexia (20.0%). The most common Grade ≥3 AE was anemia (7.7%). Adverse events led to discontinuation for 15.4% of subjects. Five subjects died within 30 days of the last dose, 4 from disease progression and 1 from respiratory depression. The maximum tolerated dose (MTD) of ibrutinib was not reached.

1.2.2.2.2. Study PCYC-1102-CA

Study PCYC-1102-CA is a Phase 1b/2, open-label, multicenter study. One hundred seventeen subjects with CLL/SLL were enrolled into 1 of 5 treatment groups, each receiving 1 of 2 fixed dose levels (420 mg/day or 840 mg/day) of ibrutinib.[32] Of the 61 subjects in Groups 1 (relapsed/refractory; 420 mg) and 3 (relapsed/refractory; 840 mg) with relapsed or refractory disease had received a median of 4 (range: 1 to 12) prior therapies, with all subjects receiving nucleoside analogs. The median age for subjects in Groups 1 and 3 was 64 years. Thirty-nine percent of subjects had an ECOG performance score of 0 and 61% had a score of 1 or 2.

Molecular, clinical, and prior treatment characteristics reflected a poor-risk population. Twenty-eight (46%) subjects from Groups 1 and 3 were considered refractory to purine analog therapy (ie, <12-month treatment-free interval following purine analog regimen). Fifty-four percent had bulky disease (defined as single lymph nodes measuring ≥5 cm). Seventy-nine percent of subjects had at least 1 molecular poor-risk feature (immunoglobulin variable heavy gene [IgVH] unmutated, del [17p], del [11q], or β2 microglobulin >3 mg/L), with 36% of subjects having del (17p).

The ORR was 67% with 2% CRs. An additional 23% of subjects had >50% shrinkage of lymphadenopathy (nodal response) and 3% had stable disease. The 840-mg cohort was stopped after comparable efficacy and safety between 420 mg and 840 mg was shown. The 12-month PFS estimate for Group 1 was 88% and for Group 3 was 82%.

Safety data are available for 114 subjects across all 5 treatment groups. The most common AEs were diarrhea (53.5%), fatigue (28.1%), nausea (24.6%), upper respiratory tract infection (22.8%), cough (22.8%), and arthralgia (21.1%). The most common Grade ≥3 AEs were anemia (8.8%), neutropenia (7.0%), and thrombocytopenia (7.0%). Four subjects died within 30 days of last dose, 2 from sepsis and 2 from pneumonia.

1.2.2.2.3. Study PCYC-1108-CA

Study PCYC-1108-CA is an ongoing combination CIT Phase 1b/2 study which has completed enrollment. Among 33 subjects with relapsed and refractory CLL/SLL enrolled, 30 have received BR and ibrutinib and 3 have received FCR and ibrutinib. The FCR cohort enrollment was suspended due to slow enrollment related to the lack of subjects at participating sites with relapsed CLL in whom the FCR regimen was considered appropriate. For subjects receiving the BR combination, bendamustine 70 mg/m^2 was administered on Day 1 and Day 2, combined with rituximab at 375 mg/m^2 on Day 1 of Cycle 1 and 500 mg/m^2 on Day 1 for all subsequent courses for a maximum of 6 cycles. Ibrutinib was administered as a continuous daily oral dose of 420 mg. The median number of prior therapies was 2 (range 1 to 4). There were 37% and 13% of subjects, respectively, who were considered either refractory to a purine analog-containing regimen or to BR (treatment-free interval prior to enrollment was <12 months). Bulky disease was present in 52% of subjects.

At a median follow-up of 4.9 months (range 2.7 to 8.3 months), the ORR was 90% (CR 10%, partial response [PR] 80%). Two additional subjects achieved a nodal response with residual

lymphocytosis. Responses appear to be independent of high-risk clinical or genomic features. Ninety percent of subjects currently remain on study. Three subjects have discontinued, 2 for progressive disease (PD) and 1 in pursuit of a stem cell transplant.

For the 30 subjects who received the combination of ibrutinib and BR, the most common AEs were diarrhea (70%), nausea (57%), fatigue (37%), thrombocytopenia, headache, and neutropenia (27% each). The most commonly reported Grade ≥3 AEs were neutropenia (23%), fatigue, rash, thrombocytopenia, and tumor lysis syndrome (TLS) (7% each). Serious adverse events (SAEs) (regardless of attribution) were reported for 10% of subjects and included cellulitis, TLS, and febrile neutropenia. There have been no discontinuations due to AEs and no deaths on study.

1.2.2.2.4. Study PCYC-1109-CA

Study PCYC-1109-CA is an ongoing Phase 1b/2 study combining ibrutinib with ofatumumab. Based on preliminary data from 27 subjects with relapsed or refractory CLL/SLL/prolymphocytic leukemia (PLL) (n=24) or Richter's transformation (RT, n=3), all subjects achieved a PR (100% ORR). Safety data are available for 47 subjects. The most common AEs have been contusion (42.6%), diarrhea (31.9%), peripheral sensory neuropathy (25.5%), and stomatitis (21.3%). The most common AE of Grade ≥3 was anemia (10.6%). Three subjects died within 30 days of last dose, 1 from pneumonia and myocardial infarction, 1 from subdural hematoma, and 1 from pneumonia. The median follow-up is 6.5 months (range: 5.3 to 10.2 months).

1.2.2.2.5. Summary of Efficacy of Ibrutinib in CLL

Efficacy results from Studies PCYC-04753, PCYC-1102-CA, PCYC-1108-CA, and PCYC-1109-CA demonstrate that ibrutinib has robust activity in CLL both as a single agent and in combination. All studies included patients with relapsed and refractory disease. Response rates for the 4 studies were independent of high-risk factors or genomic features. The predictable and characteristic pattern of response, with rapid reduction in lymphadenopathy, frequent and early hematologic improvement, and transient lymphocytosis, is consistent with the established anti-homing, anti-adhesion, pro-apoptotic, and anti-proliferative effects of BTK inhibition in CLL cells. Of particular note, high response rates have been demonstrated with continuing therapy in Studies PCYC-1102-CA, PCYC-1108-CA, and PCYC-1109-CA.

1.2.2.3. Treatment-related Lymphocytosis

Similar to other agents targeting B-cell receptor signaling, transient lymphocytosis is a pharmacodynamic effect of ibrutinib, in which the inhibition of BTK-mediated cellular homing and adhesion results in a mobilization of tumor cells to the peripheral blood.[45]

Upon initiation of treatment, a transient phase of increase in lymphocyte counts (ie, ≥50% increase from baseline and above absolute count 5000/μL), often associated with reduction of lymphadenopathy, has been observed in most patients (75%) with relapsed/refractory CLL/SLL treated with ibrutinib. This effect has also been observed in some patients (33%) with relapsed/refractory MCL treated with ibrutinib. This observed transient lymphocytosis is usually

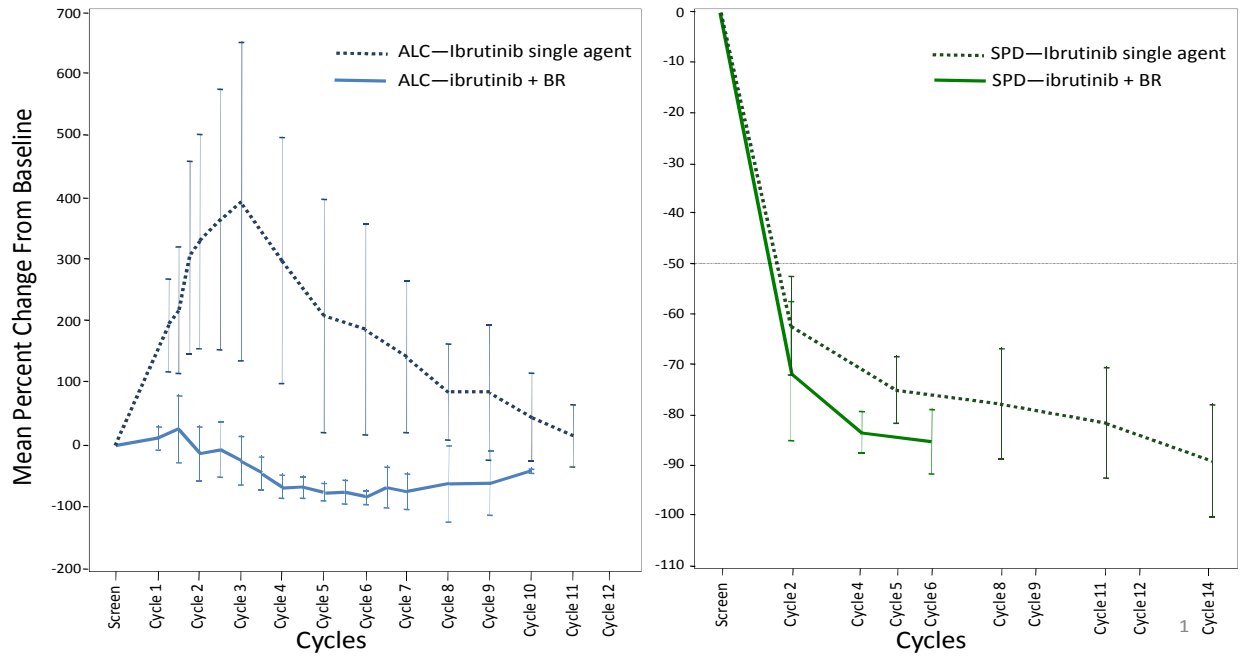
not associated with an adverse event and should not be considered progressive disease in the absence of other clinical findings. In both disease types, lymphocytosis typically occurs during the first few weeks of ibrutinib therapy (median time 1.1 weeks) and resolves within a median of 7.1 weeks in the MCL and 18.7 weeks in the CLL patients.

A substantial increase in the number of circulating lymphocytes has been observed in a subset of patients. There have been isolated cases of leukostasis reported in these patients while 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 leukapheresis as indicated. Ibrutinib may be temporarily held, and the medical monitor should be contacted.

In Study PCYC-1108-CA, treatment-related lymphocytosis was observed, although it was not as pronounced in subjects treated with ibrutinib in combination with BR compared with ibrutinib alone. Approximately one-third of the subjects have developed transient treatment-related lymphocytosis with a peak absolute lymphocyte count (ALC) greater than 50% above baseline value. In 5 (17%) of 30 subjects, the peak ALC was greater than 200% above baseline counts. The pattern of response is depicted in the following figures.

Figure 1 Pattern of Response – Ibrutinib + BR versus Single-Agent Ibrutinib: Blood Lymphocytes versus Lymph Nodes Sum of Products of Diameters: Studies PCYC-1102-CA and PCYC-1108-CA



An increase in the number of circulating lymphocytes in the peripheral blood in the setting of unequivocal improvement in at least 1 other disease-related parameter, including lymph node size, spleen size, hematologic parameters (hemoglobin and platelet count), or disease-related symptoms was not considered an indicator of PD by the investigators. This is consistent with the recommendation of the current National Comprehensive Cancer Network (NCCN) guideline (2012).[28]

1.2.2.4. Overview of Clinical Safety

The integrated safety profile of ibrutinib administered as monotherapy to 506 patients across 8 clinical studies (PCYC-04753, PCYC-1102-CA, PCYC-1104-CA, and PCYC-1106-CA, PCI32765MCL2001, PCYC-1111-CA, PCYC-1117-CA, and PCI-32765-JPN-101) has been evaluated. The most common treatment-emergent adverse events as of 06 April 2013 were diarrhea (42.1%), fatigue (33.8%), nausea (26.1%), cough (20.2%), and peripheral edema (18.6%). Grade 3 or higher adverse events were experienced by 60.7% of patients, the most common (> 2%) of which were hematologic in nature: neutropenia (9.7%), thrombocytopenia (6.5%), and anemia (4.9%). Pneumonia (7.7%) was the most frequent nonhematologic Grade 3 or higher adverse event. Serious adverse events were experienced by 46.4% of treated patients. The only serious events occurring in more than 2% of patients were pneumonia (7.9%), atrial fibrillation (3.2%), and febrile neutropenia (2.8%).

The safety of ibrutinib administered as combination therapy to 130 subjects was evaluated in 3 clinical studies: PCYC-1108-CA, PCYC-1109-CA, and PCI-32765DBL1002 (ibrutinib administered in combination with standard R-CHOP (rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisone).

As of 06 April 2013, across these combination studies, the most common adverse event has been diarrhea (47.7%), nausea (33.1%), infusion-related reaction (29.2%), and fatigue (26.2%). Neutropenia (24.6%) has been the most common hematologic toxicity, followed by anemia (20.0%) and thrombocytopenia (19.2%). Adverse events that were Grades 3 or higher in severity were reported in 57.7% of subjects. The most common have been hematologic: neutropenia (21.5%), anemia, and thrombocytopenia (7.7% each), and febrile neutropenia (6.2%). Pneumonia (7.7%) was the most frequently reported nonhematologic Grade 3 or higher adverse event. Overall, 36.2% of treated subjects have experienced at least 1 serious adverse event. The most commonly reported serious adverse events were febrile neutropenia and pneumonia (6.2% each), cellulitis (3.8%), atrial fibrillation (3.1%), and dehydration and dyspnea (2.3% each).

There are reports of hemorrhagic events in subjects treated with ibrutinib in both monotherapy and combination clinical studies. The majority of these hemorrhagic adverse events were of Grade 1 or 2 in severity; those included contusion, epistaxis, and petechiae. Hemorrhagic events of Grade 3 or higher, including central nervous system (CNS) hemorrhage of any grade severity, occurred in 3.4% (17/506) of subjects treated in monotherapy studies and in 3.1% (4/130) of subjects treated in combination therapy studies; none were reported in the healthy volunteer studies (N=100). In the extension study, PCYC-1103-CA, 2 additional Grade 3 events associated with bleeding were reported (‘gastrointestinal haemorrhage’ and ‘haematotympanum’). Details

of these events are provided in the Investigator's Brochure.

It is not clear whether or not these events are attributable to ibrutinib. However, it is possible that treatment with ibrutinib could increase the risk of bruising or bleeding. Subjects in the current study will be monitored closely for hemorrhagic adverse events. Guidance on use of antiplatelet agents and anticoagulants is provided in Section 8.3.

Other malignant diseases have been observed in subjects who have been treated with ibrutinib, including skin cancers, adenocarcinomas, and other hematologic malignancies. It is not clear whether or not these events are attributable to ibrutinib. Subjects in the current study will be monitored for other malignancies.

Mild to moderate rashes have been observed with ibrutinib alone or in combination with other drugs. A single case of Stevens-Johnson Syndrome (SJS) was reported in a male subject with CLL treated with ibrutinib 420 mg/day. The subject was also receiving multiple concomitant medications known to be associated with SJS. Subjects should be monitored closely for signs and symptoms suggestive of SJS.

In non-randomized clinical trials, infections (including sepsis, bacterial, viral, or fungal infections) were observed in subjects with MCL (≥Grade 3; 25.2%) and CLL/SLL (≥Grade 3; 37.6%). Some of these infections have been associated with hospitalization and death. Subjects should be monitored for fever and infections and appropriate anti-infective therapy should be instituted as indicated.

1.3. Overall Rationale for the Study

Although there have been impressive gains in treatment and in the understanding of the biology of CLL, the disease is incurable using chemotherapy or CIT. Stem cell transplant may be curative, but few patients are able to undergo this treatment.[20] The more relapses patients incur, the more resistant patients become to therapy.[24,27] Therefore, there is a need for further development of therapies for CLL.

2. OBJECTIVES AND HYPOTHESIS

2.1. Objectives

Primary Objective

The primary objective is to determine whether the addition of ibrutinib to BR significantly improves PFS compared with BR in subjects with relapsed or refractory CLL/SLL.

Secondary Objectives

The secondary objectives are:

- To evaluate the safety of ibrutinib in combination with BR
- To evaluate the ORR (CR + complete response with incomplete marrow recovery (CRi) + PR + nodular partial response [nPR])
- To evaluate the OS
- To evaluate the rate of minimal residual disease (MRD)-negative remissions
- To evaluate improvement in hematologic parameters (hemoglobin, neutrophil count, platelet count)
- To evaluate improvement of disease-related symptoms (fatigue, night sweats, weight loss, fever, and abdominal discomfort due to splenomegaly)
- To evaluate patient-reported symptoms, functional status, and well-being as measured by European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ)-C30, EORTC QLQ-CLL 16, EQ-5D-5L, and Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue Scale
- To characterize the PK of ibrutinib and explore its potential effect on bendamustine and rituximab PK, the potential relationships between ibrutinib metrics of exposure with relevant clinical or biomarker information
- To examine biomarkers related to BCR and compensatory signaling pathways and explore their association with resistance to ibrutinib treatment

2.2. Hypothesis

The primary hypothesis of this study is that the addition of ibrutinib to BR compared with BR alone will significantly improve PFS in subjects with relapsed or refractory CLL/SLL.

3. STUDY DESIGN AND RATIONALE

3.1. Overview of Study Design

This is a randomized, double-blind, placebo-controlled, multicenter, Phase 3 study to determine the benefits and risks of combining ibrutinib and BR in subjects with relapsed or refractory CLL/SLL following at least 1 line of prior systemic therapy.

All subjects will receive background therapy with BR for a maximum of 6 cycles as described in Section 6. A cycle will be defined as 28 days, with the exception of Cycle 1, which will be 29 days to allow for rituximab dosing prior to bendamustine and study medication. For the purposes of this protocol, study treatment is defined as bendamustine hydrochloride, rituximab, and ibrutinib/placebo; study drug is defined as ibrutinib/placebo. Approximately 580 subjects will be randomized in a 1:1 ratio to either Treatment Arm A (placebo) or Treatment Arm B (ibrutinib 420 mg). Study medication will be administered orally once daily on a continuous schedule.

Stratification factors will include whether refractory to purine analog therapy (yes or no) and number of prior lines of therapy (1 or >1). For stratification, refractory is defined specifically as a failure to respond (ie, progressive disease [PD] or stable disease [SD]) to a purine analog or a recurrence of disease within 12 months of the last dose of purine analog therapy. Separate lines of therapy are defined as single or combination therapy regimens that are either separated by disease progression or refractory disease or by a treatment-free interval of 6 months or greater. In addition, a change of regimen due to insufficient response may be considered a separate line of therapy.

Subject participation will include a Screening Phase, a Treatment Phase, and a Follow-up Phase. The Screening Phase will be up to 30 days prior to randomization. The Treatment Phase will extend from randomization until study treatment (bendamustine, rituximab, and ibrutinib/placebo) discontinuation. Subjects will receive both BR and study medication (ibrutinib or placebo) for the first 6 cycles, and thereafter will receive study medication until disease progression or unacceptable toxicity. For subjects who discontinue BR prior to completing 6 cycles, treatment with study medication will continue. The Follow-up Phase will begin once a subject discontinues study treatment. Subjects who discontinue for reasons other than disease progression will continue to have disease evaluations according to the Time and Events Schedule. The Follow-up Phase will continue until death, loss to follow up, consent withdrawal, or study end, whichever occurs first. Study end is defined as when either 80% of the subjects have died or 5 years after the last subject is randomized into the study, whichever occurs first.

Assessment of tumor response and progression will be conducted in accordance with the IWCLL 2008 Guidelines.[22] The investigator will evaluate sites of disease by radiological imaging, physical examination, or other procedures as necessary, and review of hematology and clinical chemistry results. A central laboratory will perform complete blood count (CBC) testing. The primary efficacy analysis of PFS will be based on assessment by an Independent Review

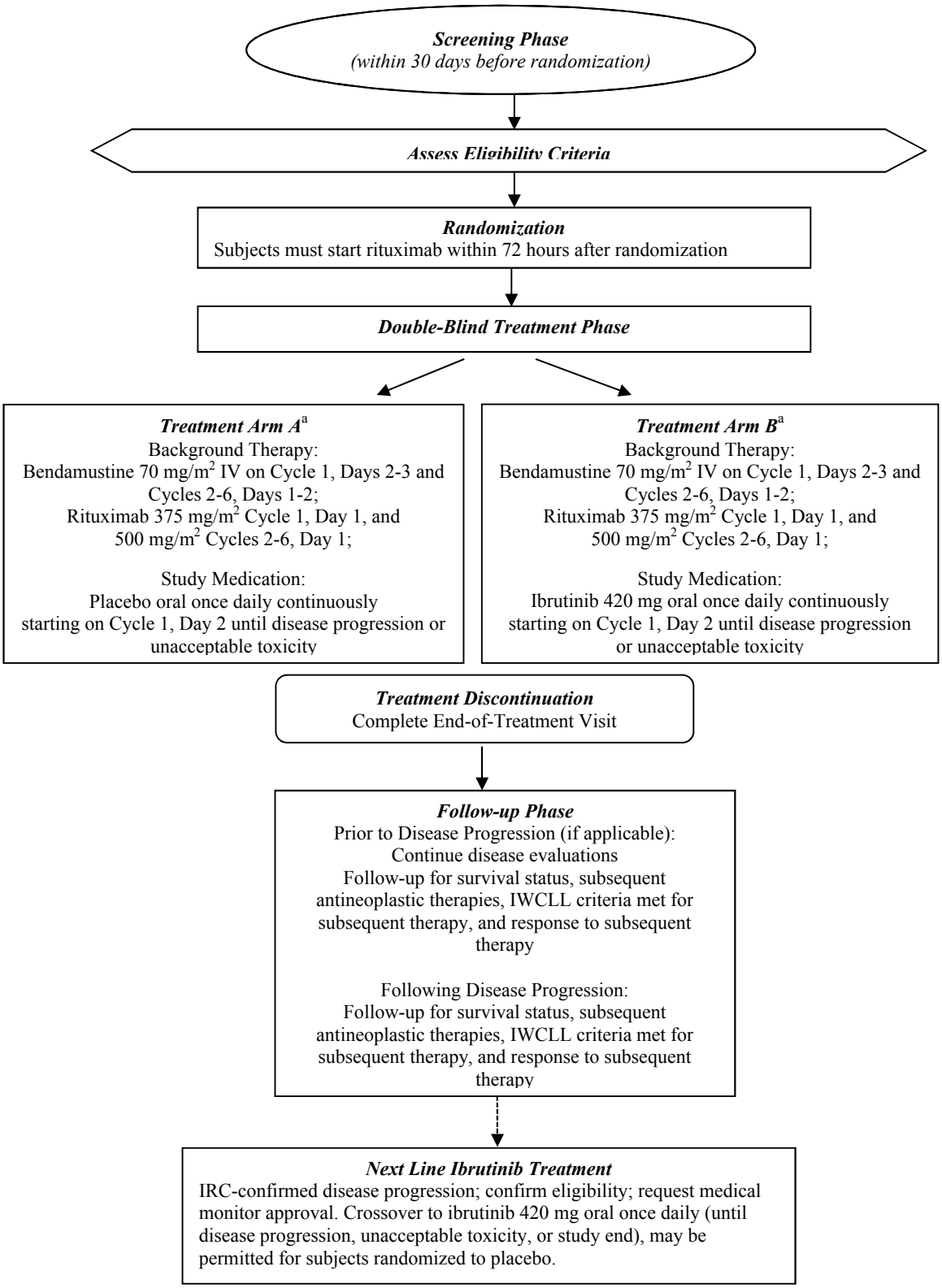
Committee (IRC). Patient-reported symptoms, functional status, and well-being will also be measured.

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

An independent Data Monitoring Committee (DMC) will be formed and constituted according to regulatory agency guidelines (see Section 11.9). One interim analysis is planned for the study (see Section 11.8).

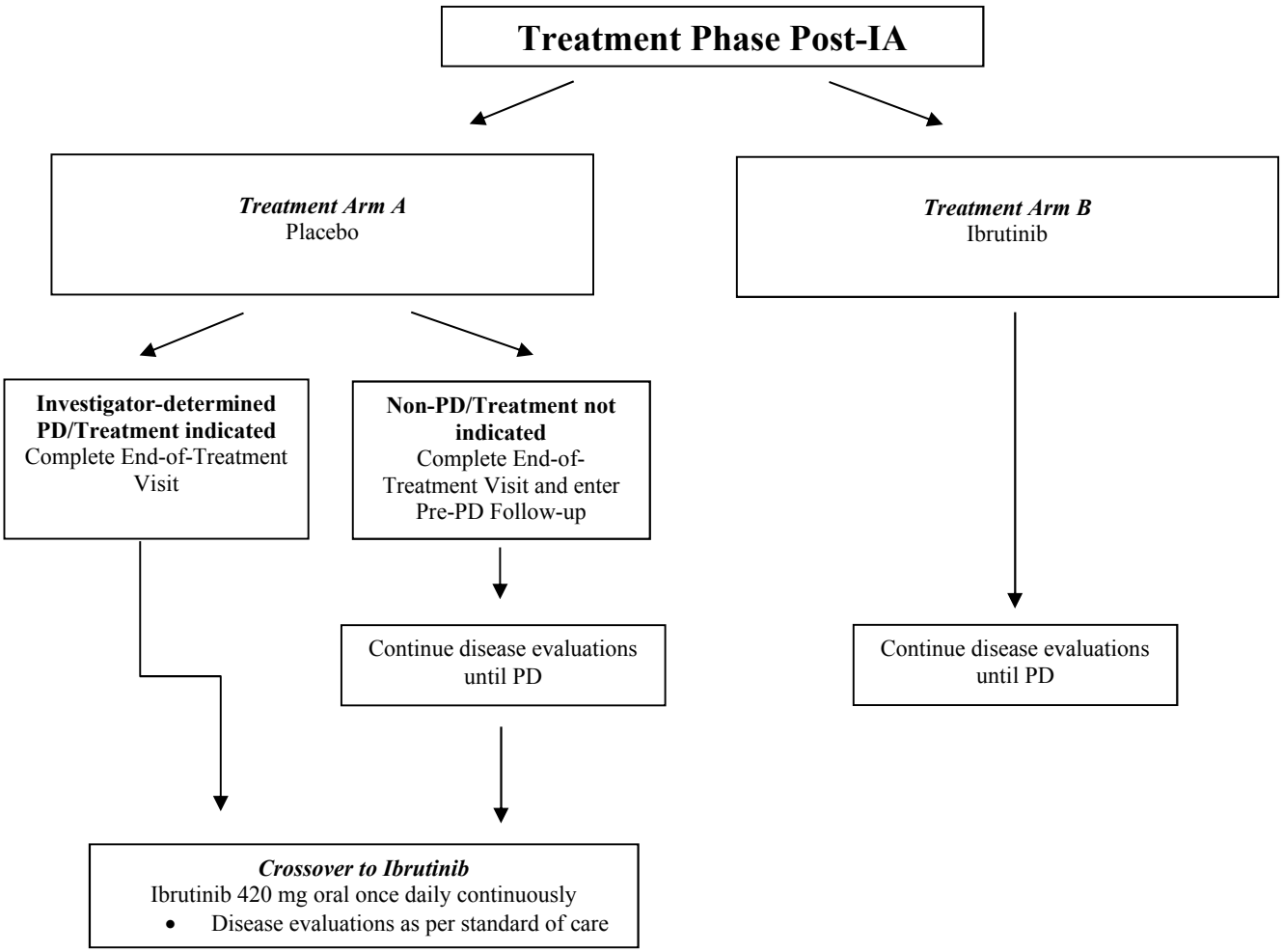
A diagram of the study design for the double-blind phase of the study is provided in Figure 2, and the study design after interim analysis is provided in Figure 3.

Figure 2 Study Design Schematic – Prior to Interim Analysis



[a] A cycle will be defined as 28 days, except for Cycle 1, which will be 29 days.

Figure 3 Study Design Schematic – Post- Interim Analysis



3.1.1. Treatment With Ibrutinib After Interim Analysis

At investigator's discretion, subjects who have received placebo in the blinded phase of the study and have disease progression or meet the IWCLL criteria for requiring subsequent anti-CLL therapy and other eligibility criteria may be offered ibrutinib treatment. These subjects will follow the Time and Events Schedule titled, "Crossover to Ibrutinib". Subjects who have received ibrutinib in the blinded phase of the study will follow the Time and Events Schedule titled "After Interim Analysis: Applies To Subjects Continuing Ibrutinib or Subjects in Follow-Up". Treatment with ibrutinib will continue until disease progression, unacceptable toxicity, withdrawal from study, or until the study end, whichever occurs earlier.

3.2. Study Design Rationale

Rationale for Background Therapy, Study Medication Dose, Randomization

Background treatment with BR will be at the dose and schedule considered standard for patients with relapsed or refractory CLL, which were based on the findings of a Phase 1b study and a subsequent Phase 2 study.[1,15] Both NCCN (Version 2012) and ESMO treatment guidelines (Version 2011) list BR as one of the recommended treatment options for patients with relapsed or refractory disease, except for patients with del (17p).[28,10]

The dose of ibrutinib for this study is based on Study PCYC-1108-CA, in which subjects were treated with ibrutinib 420 mg/day in combination with the standard 6-cycle regimen of BR. The study demonstrated promising efficacy and acceptable tolerability for this combination.

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. Blinded treatment will be used to reduce potential bias during data collection and evaluation of endpoints.

Rationale for Efficacy Endpoints, Patient-Reported Outcomes (PROs), Biomarkers

The primary endpoint of PFS has served as the basis for regulatory approvals in CLL. The secondary endpoints of ORR and OS are recommended endpoints for the clinical study evaluation of new treatments for CLL.[22] Advances in detection technologies have determined that some patients who achieve CRs have MRD as shown by the continued presence of small numbers of CLL cells. Therefore, the absence of MRD is included as a secondary endpoint.

Patient-reported outcome data are included to complement data collected by other methods. This type of data may contribute to enhanced communication of results to patients, clinicians, regulators and payers. Frequency of data collection is varied to reduce respondent burden with symptom data being collected more frequently than data related to functional status and well-being.

Inhibition of BTK tyrosine phosphorylation by ibrutinib has been shown to abrogate downstream survival pathways (eg, ERK1/2, PI3K, NF-kB, and MAPK). Inhibition by ibrutinib also interferes with activation of integrins and chemokine networks leading to interference with adhesion, migration, and homing of malignant cells.[23,38] It is anticipated that subjects with alterations in BCR signaling components or activation of alternative signaling pathways may have differential response to treatment. The biomarker evaluations within this study will identify biomarker classifiers associated with resistance to ibrutinib in subjects with CLL. The results may assist in the development of this drug in these and other indications.

4. SUBJECT SELECTION

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 below, then the investigator should consult with the appropriate sponsor representative before enrolling a subject in the study. For a discussion of the statistical considerations of subject selection, refer to Section 11.2, Sample Size Determination.

Entry criteria for subjects in Treatment Arm A (placebo) who have disease progression and may be eligible to crossover to receive treatment with ibrutinib are provided in Section 9.1.5.

4.1. Inclusion Criteria

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

1. 18 years of age or older;
2. Criterion modified per amendment
   - 2.1. Criterion modified per amendment
   - 2.2. Diagnosis of CLL or SLL that meets published diagnostic criteria:[22]
     a. Monoclonal B-cells (either kappa or lambda light chain restricted) that are clonally co-expressing at least one B-cell marker (CD19, CD20, or CD23) and CD5.
     b. The diagnosis of CLL requires a history of lymphocytosis with a B-lymphocyte count ≥5,000/μL while SLL patients are characterized by the same criteria with a circulating B-lymphocyte count <5,000/μL. Prolymphocytes may comprise no more than 55% of blood lymphocytes.
     c. There is no evidence of cyclin D1 rearrangement or BCL-1 overexpression. This evidence is required only when the diagnosis of CLL/SLL is not otherwise clear.
3. Active disease meeting at least 1 of the following IWCLL 2008 criteria for requiring treatment:
   a. Evidence of progressive marrow failure as manifested by the development of, or worsening of, anemia or thrombocytopenia;
   b. Massive (ie, at least 6 cm below the left costal margin), progressive, or symptomatic splenomegaly;

c. Massive nodes (ie, at least 10 cm in longest diameter), progressive, or symptomatic lymphadenopathy;

d. Progressive lymphocytosis with an increase of more than 50% over a 2-month period or a lymphocyte doubling time (LDT) of less than 6 months (which may be extrapolated). Lymphocyte doubling time can be obtained by linear regression extrapolation of ALCs obtained at intervals of 2 weeks over an observation period of 2 to 3 months. For patients with initial blood lymphocyte counts of less than 30 x 109/L (30,000/μL), LDT should not be used as a single parameter to define indication for treatment. In addition, factors contributing to lymphocytosis or lymphadenopathy other than CLL (eg, infections) should be excluded;

e. Constitutional symptoms, defined as 1 or more of the following disease-related symptoms or signs:

1) Unintentional weight loss >10% within the previous 6 months prior to 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; or

4) Night sweats for more than 1 month without evidence of infection.

4. Measurable nodal disease by computed tomography (CT). Measurable nodal disease is defined as at least one lymph node >1.5 cm in longest diameter in a site that has not been previously irradiated. An irradiated lesion may be assessed for measurable disease only if there has been documented progression in that lesion since radiotherapy has ended;

5. Criterion modified per amendment

5.1. Relapsed or refractory CLL or SLL following at least 1 prior line of systemic therapy, consisting of at least 2 cycles of a chemotherapy-containing regimen;

6. ECOG Performance Status score of 0 or 1 (Attachment 1);

7. Criterion modified per amendment.

7.1. Criterion modified per amendment.

7.2. Hematology values within the following limits:

a. Absolute neutrophil count (ANC) ≥1 x 10^9/L (ie, ≥1000/μL).

b. Platelets ≥50 x 10^9/L (ie, ≥50,000/μL) and more than 7 days since last transfusion.

8. Criterion modified per amendment.

8.1. Biochemical values within the following limits:

a. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2.5 x upper limit of normal (ULN).

b. Total bilirubin ≤1.5 x ULN (unless due to Gilbert's syndrome).

c. Creatinine ≤2 x ULN and estimated glomerular filtration rate (GFR [Cockcroft-Gault]) ≥40 mL/min.

9. Criterion modified per amendment

   9.1. Women of childbearing potential and men who are sexually active with a woman of childbearing potential must be practicing a highly effective method of birth control during and after the study, consistent with local regulations regarding the use of birth control methods for subjects participating in clinical studies. Men must agree to not donate sperm during and after the study. For females, these restrictions apply for 6 months after last dose of bendamustine, 12 months after the last dose of rituximab or 1 month after the last dose of study medication, whichever is later. For males, these restrictions apply for 6 months after the last dose of bendamustine, 12 months after the last dose of rituximab, or 3 months after the last dose of study medication, whichever is later.

10. Women of childbearing potential must have a negative serum (β-human chorionic gonadotropin [β-hCG]) or urine pregnancy test at screening.
11. Must sign (or their legally-acceptable representatives must sign) an informed consent document indicating that they understand the purpose of and procedures required for the study and are willing to participate in the study.

4.2. Exclusion Criteria

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

1. Recent therapeutic interventions including:
   a. Prior nitrosoureas within 6 weeks prior to randomization.
   b. Therapeutic anticancer antibodies within 4 weeks prior to randomization.
   c. Radio- or toxin-immunoconjugates or immunotherapy within 10 weeks prior to randomization.
   d. All other chemotherapy, radiation therapy within 3 weeks prior to randomization.
   e. Major surgery within 4 weeks prior to randomization.
2. Prior treatment with ibrutinib or other BTK inhibitors or prior randomization in any other clinical study evaluating ibrutinib.
3. Concurrent enrollment in another therapeutic investigational clinical study.
4. The presence of deletion of the short arm of chromosome 17, ie, del (17p13.1), as defined by del (17p) in ≥20% of cells examined on any pretreatment fluorescence in situ hybridization (FISH) or cytogenetics evaluation. Cytogenetic status results must be documented in patient records prior to randomization.
5. Criterion modified per amendment.

   5.1. Patients previously treated with a bendamustine-containing regimen who did not achieve a response or who relapsed and required treatment within 24 months of treatment with that regimen.

6. Subjects for whom the goal of therapy is tumor debulking prior to stem cell transplant.

7. Received a hematopoietic stem cell transplant.
8. Known central nervous system (CNS) leukemia/lymphoma or Richter's transformation.
9. Patients with uncontrolled autoimmune hemolytic anemia (AIHA) or autoimmune thrombocytopenia (ITP) (Coombs positivity in absence of hemolysis is not an exclusion).
10. Chronic use of corticosteroids in excess of prednisone 20 mg/day or its equivalent.
11. History of prior malignancy, except:
    a. Malignancy treated with curative intent and with no known active disease present for ≥3 years 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.
12. History of stroke or intracranial hemorrhage within 6 months prior to randomization; or clinically significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of screening; or any Class 3 (moderate) or Class 4 (severe) cardiac disease as defined by the New York Heart Association Functional Classification.
13. Criterion modified per amendment
    13.1. Requires anticoagulation with warfarin or equivalent vitamin K antagonists (eg, phenprocoumon).
14. Known history of Human Immunodeficiency Virus (HIV) or Hepatitis C, or active infection with Hepatitis B or Hepatitis C.
15. Any 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, interfere with the absorption or metabolism of ibrutinib capsules, or put the study outcomes at undue risk.
16. A woman who is pregnant or breast feeding, or a man who plans to father a child while enrolled in this study or within 3 months after the last dose of study drug.
17. Requires treatment with strong CYP3A4/5 inhibitors (Attachment 3).

NOTE: Investigators should ensure that all study enrollment criteria have been met at screening. If a subject's status changes (including laboratory results or receipt of additional medical records) after screening but before randomization such that they he or she no longer meets all eligibility criteria, then 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 be willing and able to adhere to the following prohibitions and restrictions during the course of the study to be eligible for participation. Subjects should avoid use of foods or beverages containing grapefruit or Seville oranges, as these contain certain ingredients that inhibit CYP3A4/5. Prohibited medications and precautions with concomitant 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 study medication (ibrutinib/placebo):

- For any surgery or invasive procedure requiring sutures or staples for closure, study medication should be held at least 7 days prior to the intervention and should be held 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), study medication 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 study medication for these procedures.
- For emergency procedures, study medication 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 AND BLINDING

Treatment Allocation

Procedures for Randomization and Stratification

Central randomization will be implemented in this study. Subjects will be randomly assigned to 1 of 2 treatment groups in a 1:1 ratio 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 randomly permuted blocks and will be stratified by purine analog refractory status (yes vs. no) and number of prior lines of therapy (1 or >1). The interactive web response system (IWRS) will assign a unique treatment code, which will dictate the treatment assignment and matching study drug 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 enter the relevant subject details to uniquely identify the subject.

Blinding

The investigator will not be provided with randomization codes. The codes will be maintained within the IWRS, which has the functionality to allow the investigator to break the blind for an individual subject.

Under normal circumstances, the blind should not be broken until all subjects have completed the study and the database is finalized. Otherwise, the blind should be broken only if specific emergency treatment/course of action would be dictated by knowing the treatment status of the subject. In such cases, the investigator may in an emergency determine the identity of the treatment by contacting the IWRS. It is recommended that the investigator contact the sponsor or its designee if possible to discuss the particular situation, before breaking the blind. Telephone contact with the sponsor or its designee will be available 24 hours per day, 7 days per week. In the event the blind is broken, the sponsor must be informed as soon as possible. The date, time, and reason for the unblinding must be documented by the IWRS, in the appropriate section of the case report form (CRF), and in the source document. The documentation received from the IWRS indicating the code break must be retained with the subject's source documents in a secure manner. Subjects who have had their treatment assignment unblinded should continue to return for scheduled evaluations and with sponsor approval may continue study treatment.

In general, randomization codes will be disclosed fully only if the study is completed and the clinical database is closed. However, a subject with IRC-confirmed disease progression who meets the eligibility criteria for next-line ibrutinib therapy may be unblinded by a medical monitor separate from the study team. If the subject is found to be randomized to placebo (Treatment Arm A), the investigator will be informed of the subject’s eligibility and the subject will be allowed to start treatment with next-line ibrutinib, 420 mg daily. After positive interim analysis, the study is unblinded and investigators informed of subject treatment allocation. Subjects receiving placebo may be eligible for ibrutinib treatment, according to the criteria in Section 9.1.5.

6. DOSAGE AND ADMINISTRATION

All subjects will receive BR as the background therapy for a maximum of 6 cycles, as shown below. A cycle will be defined as 28 days, with the exception of Cycle 1, which will be 29 days to allow for rituximab dosing prior to bendamustine and study medication.

- Bendamustine hydrochloride: 70 mg/m^2 infused IV over 30 minutes on Cycle 1, Days 2 and 3, and on Cycles 2-6, Days 1 and 2 for up to 6 cycles, unless progression of disease or unacceptable toxicity is encountered prior to Cycle 6.
- Rituximab, 375 mg/m^2 in the first cycle, Day 1, and 500 mg/m^2 in Cycles 2 through 6, Day 1.

If a rituximab infusion is interrupted on Day 1 due to toxicity and has to be split over a 2-day period in Cycle 1, bendamustine may be administered on Days 3 and 4 or immediately after the subject's recovery from toxicity (if recovery occurs later). The administration of study medication should start on the same day as bendamustine. A similar approach to dosing may be used for subsequent cycles.

Subjects will be randomized 1:1 to receive either treatment arm A or B. Treatment will continue until disease progression or unacceptable toxicity. Ibrutinib or placebo will be self administered at home.

Treatment Arm A:

Placebo (3 capsules) will be administered orally once daily continuously.

Treatment Arm B:

Ibrutinib 420 mg (3 x 140-mg capsules) will be administered orally once daily continuously.

6.1. Bendamustine and Rituximab Administration

Investigators should refer to the package inserts for the storage and handling, and detailed instructions on the administration of bendamustine hydrochloride and rituximab, respectively.[40,41] BR is administered IV, per institutional standards, at the dosages described above. BR treatment will be administered for a maximum of 6 cycles in absence of disease progression or treatment-limiting toxicity.

6.2. Study Drug Administration

Subjects will be instructed to take 3 capsules of ibrutinib (for a dose of 420 mg) or placebo orally once daily. The capsules are to be taken around the same time each day with approximately 240 mL of water (ie, 8 ounces). The capsules should be swallowed intact and subjects should not attempt to open capsules or dissolve them in water. On the days subjects receive both study medication and BR, placebo or ibrutinib will be administered after the CIT infusions. Subjects should refrain from taking study medication on the morning of study visits designated for pharmacokinetic sampling until instructed to do so at the site.

If a dose 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.

6.3. Dose Modification

Doses of bendamustine hydrochloride and rituximab should be reduced or held in accordance with the dose modification guidelines in the respective product labels, as described below.[40,41]

Bendamustine hydrochloride

Bendamustine hydrochloride administration should be delayed in the event of Grade 4 hematologic toxicity or clinically significant Grade ≥2 non-hematologic toxicity. Once non-hematologic toxicity has recovered to Grade ≤1, bendamustine hydrochloride can be reinitiated at the discretion of the investigator. For hematologic events, bendamustine hydrochloride can be reinitiated after blood counts have improved (ANC ≥1 x 10^9/L [≥1,000/μL], platelets ≥50 x 10^9/L [≥50,000/μL]), at the discretion of the investigator.

In addition, dose reduction may be warranted as follows:

- Dose modifications for hematologic toxicity: for Grade ≥3 toxicity, the dose may be reduced to 50 mg/m^2 on Days 1 and 2 of each cycle. If Grade ≥3 toxicity recurs, the dose may be reduced to 25 mg/m^2 on Days 1 and 2 of each cycle.
- Dose modifications for non-hematologic toxicity: for clinically significant Grade ≥3 toxicity, the dose may be reduced to 50 mg/m^2 on Days 1 and 2 of each cycle.

Dose re-escalation in subsequent cycles may be considered at the discretion of the investigator.

Withholding of bendamustine hydrochloride administration should be considered in the event of AST or ALT value >2.5 X ULN or total bilirubin value >1.5 X ULN.

If bendamustine hydrochloride is discontinued for toxicity, then treatment with rituximab may be continued.

Rituximab

There will be no dose reductions for rituximab. Rituximab should be held for any Grade 4 toxicity or other clinically significant events, as detailed in the product label. Particular attention should be paid to the Warnings and Precautions sections. Detailed dosing instructions for infusion reactions are provided in the product label.[41]

If rituximab is discontinued for toxicity, then treatment with bendamustine hydrochloride may be continued.

Study Medication (Ibrutinib or placebo)

Treatment with study medication (ibrutinib/placebo) should be held for any unmanageable, potentially study drug-related toxicity that is Grade ≥3 in severity. Study medication may be held for a maximum of 28 consecutive days, unless reviewed and approved by the sponsor. Study medication should be discontinued permanently in the event of a toxicity lasting more than 28 days. No dose escalation of study medication (above 420 mg) is allowed in this study. The

actions in the table below should be taken for the following drug-related toxicities. Changes must be recorded in the Dosage Administration CRF:

- Grade 4 neutropenia (ANC <0.5 x 10^9/L [ie, <500/μL]): If receiving study medication only, actions in the table below should be taken immediately. If receiving concurrent BR and study medication, action should be taken if the Grade 4 neutropenia persists for >14 days. Neutrophil growth factors are permitted per American Society of Clinical Oncology (ASCO) guidelines or according to the institution's guidelines and use must be recorded in CRF.
- Grade 3 thrombocytopenia (platelets <50 x 10^9/L [ie, <50,000/μL]) in the presence of significant bleeding; or in subjects with baseline thrombocytopenia a platelet decrease of 50% to 74% from baseline in the presence of significant bleeding.
- Grade 4 thrombocytopenia (platelets <25 x 10^9/L [ie, <25,000/μL]); or in subjects with baseline thrombocytopenia a decrease of >75% from baseline or <20 x 10^9/L (ie, <20,000/μL), whichever is higher.
- Grade 3 or 4 nausea, vomiting, or diarrhea (if persistent despite optimal antiemetic or anti-diarrheal therapy) or any other Grade 4 toxicity or any unmanageable Grade 3 toxicity.

Occurrence	Action
1st	Hold study medication until recovery to Grade ≤1 or baseline; may restart at original dose level
2nd	Hold study medication until recovery to Grade ≤1 or baseline; restart at 1 dose level lower (280 mg daily)
3rd	Hold study medication until recovery to Grade ≤1 or baseline; restart at 1 dose level lower (140 mg daily)
4th	Discontinue study medication
Note: For hematologic events that occurred while the subject was receiving concurrent BR and study medication, study medication may be re-initiated when BR is initiated after the counts have improved (ie, ANC ≥1,000/μL and platelets ≥50,000/μL).	

If ibrutinib/placebo is discontinued for toxicity, then treatment with bendamustine hydrochloride and rituximab may be continued.

Refer to Section 8.3 for subjects requiring the initiation of anticoagulants while receiving study medication, and for instructions on dose modifications or dose holds during concomitant administration of CYP3A4/5 inhibitors or inducers. Refer to Section 4.3 for guidance on dose delays during the perioperative period for subjects who require surgical intervention or an invasive procedure while receiving study medication.

7. TREATMENT COMPLIANCE

The investigator or designated study personnel will maintain a log of all study drug dispensed and returned. Drug supplies for each subject will be inventoried and accounted for throughout the study. On pharmacokinetic sampling days for study medication only, the timing of meals in relation to the drug intake will also be recorded.

The study drug is to be prescribed only by the principal investigator or a qualified physician listed as a subinvestigator on required forms (eg, FDA Form 1572). 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 drug are provided in the Site Investigational Product Procedures Manual. Administration of the study drug must be recorded in the subject's source documentation. The study drug may not be used for any purpose other than that outlined in this protocol, including other human studies, animal investigations, or in vitro testing.

8. PRESTUDY AND CONCOMITANT THERAPY

All prestudy antineoplastic therapies, including those since diagnosis of CLL/SLL, must be recorded at screening.

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 (ie, bendamustine, rituximab, and ibrutinib/placebo).

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 Medications

Antiemetics are permitted if clinically indicated. Standard supportive care medications are permitted, including pre-medication for rituximab and bendamustine infusions per the rituximab and bendamustine package inserts, respectively. Use of neutrophil growth factors (filgrastim and pegfilgrastim) is permitted per the ASCO guidelines or according to the institution's guidelines.[34] Use of anti-microbial prophylaxis (eg, pneumocyctis pneumonia prophylaxis with sulfamethoxazole and trimethoprim or equivalent), according to the institution's guidelines, is strongly recommended.

For subjects considered at risk for tumor lysis syndrome (TLS):

Subjects with more than 1 of the factors listed below are considered to be at increased risk of TLS and should be considered for hydration and treatment with a uric acid-lowering agent as well as for frequent monitoring of tumor lysis associated signs and symptoms. Uric-acid lowering agents may include xanthine oxidase inhibitor allopurinol or Uloric [febuxostat] with or without rasburicase per the drug product package inserts.

- Serum creatinine ≥1.5 x ULN or calculated creatinine clearance <60 mL/min
- White blood cell (WBC) ≥50,000/μL
- Uric acid ≥450 μmol/L or 7.5 mg/dL
- Bulky disease (eg, lymph node >10 cm or massive splenomegaly)
- Elevated LDH >2 x ULN

For subjects with an increased risk of TLS, rituximab may be split over a 2-day period in Cycle 1.

For subjects considered at risk for leukostasis:

A high number of circulating lymphocytes (>400,000/μL) may confer increased risk; these patients should be closely monitored. Administer supportive care such as hydration and/or leukapheresis as indicated. Ibrutinib may be temporarily held, and medical monitor should be contacted.

8.2. Prohibited Medications

The following medications are prohibited during the treatment phase of the study: any chemotherapy (other than BR), anticancer immunotherapy, corticosteroids (at dosages equivalent to prednisone >20 mg/day), experimental therapy, and radiotherapy. Corticosteroids are permitted as premedication for administration of rituximab or for the management of hypersensitivity as per institutional policy. In addition, short courses (<14 days) of corticosteroids for non-cancer related medical reasons (eg, treatment for autoimmune cytopenias) are permitted at doses not exceeding 100 mg/day of prednisone or equivalent.

8.3. Precautions with Concomitant Medications

Concomitant Use of Ibrutinib/Placebo and CYP3A4/5 Inhibitor/Inducers

Ibrutinib is metabolized primarily by CYP3A4/5. Co-administration of ibrutinib with strong CYP3A4/5 inducers (such as carbamazepine and rifampin) can decrease ibrutinib plasma concentrations and should be avoided. Co-administration of ketoconazole, a strong CYP3A4/5 inhibitor, in 18 healthy subjects, increased dose normalized exposure for C_{max} and $AUC_{0\text{-last}}$ of ibrutinib by 29- and 24-fold, respectively. However, in 38 subjects treated with mild and/or moderate CYP3A4/5 inhibitors the ibrutinib exposure (AUC) was ≤2-fold the upper limit of the range of 76 subjects not treated concomitantly with CYP3A4/5 inhibitors. Clinical safety data in subjects treated with weak, moderate, or strong CYP3A4/5 inhibitors did not reveal meaningful increases in toxicities. Since no exposure data are available in patients treated concomitantly with strong inhibitors of CYP3A4/5 (eg, ketoconazole, indinavir, nelfinavir, ritonavir, saquinavir, clarithromycin, telithromycin, itraconazole, and nefazadone), these inhibitors should be avoided. If ibrutinib must be administered with a strong inhibitor, the sponsor's Medical monitor should be consulted before use, and a dose reduction of ibrutinib to 140 mg daily or a temporary hold of ibrutinib should be considered. Subjects should be monitored for signs of ibrutinib toxicity. If a moderate CYP3A inhibitor must be used, reduce ibrutinib treatment to 140 mg for the duration of the inhibitor use. For subjects who are already on a moderate CYP3A inhibitor concomitantly with ibrutinib without significant toxicity, the investigator may consider the overall risk-benefit to determine if a dose reduction of ibrutinib is appropriate. Avoid grapefruit and Seville oranges during ibrutinib treatment, as these contain moderate inhibitors of CYP3A4/5 (see Section 6.3).

Examples of inhibitors, inducers, and substrates can be found in Attachment 3 and at http://medicine.iupui.edu/clinpharm/ddis/table.aspx.[43]

Drugs That Have Their Plasma Concentrations Altered by Ibrutinib

In vitro studies indicated that ibrutinib is a weak inhibitor of CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5. The dihydrodiol metabolite of ibrutinib is a weak inhibitor of CYP2B6, CYP2C8, CYP2C9, and CYP2D6. Both ibrutinib and the dihydrodiol metabolite are at most weak inducers of CYP450 isoenzymes in vitro. Therefore, it is unlikely that ibrutinib has any clinically relevant drug-drug interactions with drugs that may be metabolized by the CYP450 enzymes.

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, co-administration of narrow therapeutic index P-gp substrates (eg, digoxin) with ibrutinib may increase their blood concentration and should be used with caution and monitored closely for toxicity.

Concomitant Use of Ibrutinib/Placebo and QT Prolonging Agents

Any medications known to cause QT prolongation should be used with caution; periodic monitoring with ECGs and electrolytes should be considered and, if needed, the medical monitor should be contacted.

Concomitant Use of Ibrutinib/Placebo and Antiplatelet Agents and Anticoagulants

Warfarin or other vitamin K antagonists (eg, phenprocoumon) should not be administered concomitantly with ibrutinib. Supplements such as fish oil and vitamin E preparation should be avoided. Use ibrutinib with caution in subjects requiring other anticoagulants or medications that inhibit platelet function. Subjects with congenital bleeding diathesis have not been studied. 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 requiring the initiation of therapeutic anticoagulation therapy (other than warfarin or a vitamin K antagonist) during the course of the study should have treatment with study medication held, the sponsor's medical monitor should be contacted, and study medication should not be restarted until the subject is clinically stable and the re-initiation of study medication is approved by the sponsor's medical monitor. Subjects should be observed closely for signs and symptoms of bleeding. No dose reduction is required when study medication is restarted.

8.4. Subsequent Therapies

Administration of other therapies for CLL after study treatment should not be initiated until progressive disease has been established according to the criteria described in Section 9.2.1.4. If clinically appropriate, new anticancer therapy should be withheld until confirmation of progressive disease by the IRC. Any subsequent therapy for CLL (including start and end date and best response) should be documented in the CRF.

9. STUDY EVALUATIONS

9.1. Study Procedures

9.1.1. Overview

The study is divided into a Screening Phase, a Double-blind Treatment Phase, and a Follow-up Phase. The Time and Events Schedule summarizes the frequency and timing of efficacy, PRO, pharmacokinetic, biomarker, and safety measurements applicable to this study.

All visit-specific PRO assessments during a visit should preferably be conducted before any tests, procedures, or other consultations for that visit to prevent influencing subject perceptions. PRO assessments will be captured electronically and preprogrammed in the appropriate sequence. 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 will be used for grading hematologic adverse events (see Section 12.1.3).

Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or 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 335 mL within the first year. For a subset of subjects at selected sites, an additional 40 mL of blood will be drawn in the first year to explore the potential effect of ibrutinib on bendamustine and rituximab PK. Following the first year, the maximum amount of blood drawn will not exceed 25 mL every 12 weeks, and is estimated at 32 mL for the end-of-treatment visit. Repeat or unscheduled samples may be taken for safety reasons. Detailed information is provided in Attachment 4.

9.1.2. Screening Phase

Screening procedures will be performed up to 30 days before randomization. All subjects must sign an informed consent form 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 Time and Event Schedule. This evaluation will include a complete medical history, including confirmation of CLL/SLL diagnosis, staging at study entry (Attachment 2), key features of disease, and all prior cancer therapy. A sponsor review of prior therapy and active disease status per ICWLL criteria must occur before randomization is approved. Details of the approval process will be provided to sites as a separate document.

Concomitant medication and AEs will be recorded starting with the signing of the study informed consent. For women of childbearing potential, a urine or serum beta-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.

A CBC, full physical examination, and CT will occur as part of the disease evaluation. Results of radiologic assessments obtained prior to signing the informed consent as part of the subject's standard of care may be used for this study if performed within 30 days before randomization. Subsequent assessments performed throughout the study must use the same method of assessment per subject. A bone marrow biopsy, and an aspirate or peripheral blood sample are 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. All subjects will have a bone marrow aspiration or peripheral blood draw performed locally to assess the cytogenetic profile using the standard CLL FISH probes to detect abnormalities in chromosomes 13q, 12, 11q, and 17p. In addition, immunophenotyping should be performed on the aspirate or blood sample. Conventional karyotype evaluations are optional; FISH is required. Results will be collected in the CRF and subjects with ≥20% of cells with del (17p) will not be eligible to participate in the study. For subjects with SLL, a lymph node biopsy may be used for immunophenotyping, morphology, and FISH testing to confirm the diagnosis.

9.1.3. Double-Blind Treatment Phase

The double-blind Treatment Phase will begin at randomization and will continue until disease progression, unacceptable toxicity, or other reasons as described in Section 10. Subjects must start rituximab within 72 hours after randomization. The latest measurements taken on Day 1 of Cycle 1 before administration of study treatment or at screening will be defined as the baseline values. Central laboratory values that are obtained prior to Cycle 1, Day 1 should be repeated in the event that they are >48 hours old. An additional local laboratory sample should be taken to ensure the eligibility criteria are still met for hematology and chemistry values within 48 hours prior to dosing.

The subject will report to the study site on Day 1 of each cycle for study-related procedures outlined in the Time and Events Schedule. Clinical evaluations and laboratory studies may be repeated more frequently, if clinically indicated. When all evaluations have been completed, and it has been determined that the subject can continue treatment, sufficient treatment will be dispensed. Instructions for proper self-administration of study drug and storage conditions will be reviewed. If a subject shows signs of progression on physical examination or laboratory assessment, the subject may continue study treatment until progression is confirmed by CT scan. If progressive disease is diagnosed, then the subject will discontinue study treatment, complete the End-of-Treatment Visit 30 days (+7-day window) after the last dose of study treatment, and enter the Follow-up Phase.

End of Treatment

An End-of-Treatment Visit will be scheduled 30 days (+7-day window) after the last dose of study treatment for all subjects, including those 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 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 can be found in Section 12. Refer to the Time and Events Schedule 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 disease evaluations every 12 weeks and will be followed for survival status, recording subsequent antineoplastic therapy, the IWCLL criteria which were met requiring subsequent therapy, and response to subsequent therapy.

Following disease progression, contact will be made every 16 weeks until study end to determine:

- IWCLL criteria which were met requiring subsequent therapy and response to subsequent therapy;
- Subsequent antineoplastic therapy;
- Occurrence of any other malignancy;
- Occurrence of transformation to a more aggressive histology (Richter's transformation); and
- Survival status.

The EQ-5D-5L questionnaire will be administered as shown in the Time and Events Schedule. 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 death, loss to follow up, consent withdrawal, or study end, whichever occurs first. It is important that survival status be assessed and that the date of death is documented for each subject randomized to treatment, regardless of whether or not the subject received treatment. If the information on survival status and subsequent therapy is obtained via telephone contact, then written documentation of the communication must be available for review in the source documents. If the subject has died, then the date and cause of death will be collected and documented on the CRF.

9.1.5. Crossover to Ibrutinib Treatment

Subjects who satisfy all eligibility criteria listed below will be permitted to receive ibrutinib treatment at investigator's discretion.

Eligibility Criteria for Crossover to Ibrutinib Treatment

1. Criterion modified per amendment

   1.1 Investigator-determined disease progression OR active disease requiring treatment as per the IWCLL 2008 criteria (refer to inclusion criterion in Attachment 10)

2. Criterion deleted per amendment
3. Criterion deleted per amendment
4. Criterion modified per amendment

   4.1 Platelet count ≥30,000/μL

5. Criterion modified per amendment

   5.1 Biochemical values within the following limits:

   a. Adequate liver function indicated by total bilirubin ≤1.5 x ULN (unless due to Gilbert's syndrome) or up to 3 x ULN in the absence of other indications of liver disease.

   b. Creatinine ≤2 x ULN and estimated GFR (Cockcroft-Gault) ≥30 mL/min.

6. No uncontrolled active systemic fungal, bacterial, viral, or other infection (defined as exhibiting ongoing signs/symptoms related to the infection and without improvement, despite appropriate antibiotics or other treatment) or ongoing intravenous anti-infective treatment
7. No currently active clinically significant cardiovascular disease such as uncontrolled arrhythmia, congestive heart failure, any Class 3 or 4 cardiac disease as defined by the New York Heart Association Functional Classification, or history of myocardial infarction within 6 months prior to first dose with study drug
8. No history of stroke or intracranial hemorrhage within 6 months
9. Recovered from acute toxicities due to chemotherapy or other anti-CLL treatment. Nonhematologic toxicities have resolved to NCI CTCAE (v 4.03) Grade ≤2
10. Criterion deleted per amendment
11. Criterion modified per amendment

    11.1 No known Richter's transformation
12. Does not require or receive anticoagulation with warfarin or equivalent vitamin K antagonists (eg, phenprocoumon)
13. Criterion modified per amendment

    13.1 Women of childbearing potential and men who are sexually active with a woman of childbearing potential must be practicing a highly effective method of birth control during and after the study, consistent with local regulations regarding the use of birth control methods for subjects participating in clinical studies. Men must agree to not donate sperm during and after the study. For subjects receiving ibrutinib treatment within 12 months of stopping BR treatment, criterion 9.1 in Section 4.1 should be followed to ensure subject's compliance.
14. Must sign (or their legally-acceptable representatives must sign) an informed consent document indicating that they understand the purpose of and procedures required for the study and are willing to participate in the study.

9.2. Efficacy

Efficacy evaluations will be conducted as specified in the Time and Events Schedule 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 will focus on examination of lymph nodes, liver, and spleen.
- CBC with measurement of parameters including ALC by a central laboratory.
- CT scan of the neck, chest, abdomen, and pelvis.
- MRD: peripheral blood and bone marrow aspirate/biopsy with flow cytometry assessment(s) for MRD should be done if there is evidence of CR by clinical parameters. MRD is determined by flow cytometry (MRD negative defined as <1 CLL cell per

10,000 leukocytes). Subsequent MRD samples will continue to be obtained from peripheral blood at disease evaluation visits.

- Patient-reported symptoms, functional status, and well-being will be measured by EORTC-QLQ-C30, EORTC QLQ-CLL 16, EQ-5D-5L, and FACIT-Fatigue Scale.

For timing and scope of the efficacy evaluations following the implementation of the Amendment INT-4, refer to the Time and Events Schedule titled: "After Interim Analysis: Applies to Subjects Continuing Ibrutinib or Subjects in Follow-Up."

9.2.1. Evaluations

9.2.1.1. Radiographic Imaging Assessments[b]

During the study, disease response will 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 liver, lymph nodes, and spleen will be evaluated. All imaging should be performed according to the Image Acquisition Guidelines. Subjects who are intolerant of IV CT contrast agents may have CT scans performed with oral contrast. In the event disease progression is suspected due to physical examination or laboratory tests, a CT scan must be performed for further disease status evaluation. The subject may continue study treatment until disease progression is confirmed by CT scan. CT scans should be performed according to the Time and Events Schedule until disease progression is confirmed by the IRC, regardless of whether or not the subject remains on study treatment.

Magnetic resonance imaging (MRI) may be used to evaluate sites of disease that cannot be adequately imaged using CT (in cases where MRI is desirable, the MRI must be obtained at baseline and at all subsequent disease evaluations). For all other sites of disease, MRI studies do not replace the required neck, chest, abdomen, and pelvic CT scans. Brain MRI and lumbar puncture are required, only if clinically indicated.

9.2.1.2. Definition of Measurable and Assessable Disease

Subjects must have at least 1 measurable lymph node >1.5 cm detected by CT scan in order to participate in this study.[22] Measurable sites of disease are defined as lymph nodes, lymph node masses, or extranodal sites of lymphoma/leukemia. Each measurable site of disease must be greater than 1.5 cm in longest diameter. Measurement must be determined by imaging evaluation. All other sites of disease are considered assessable, but not measurable.

Up to 6 measurable lymph nodes (target lesions), clearly measurable in 2 perpendicular dimensions, will be followed for each subject. Measurable sites of disease should be chosen such that they are representative of the subject's disease. In addition, the selection of target lesions

[b] Following positive interim analysis, review of CT scans by the IRC is no longer required. In the event disease progression is suspected, the confirmation of disease progression will be done by the study responsible medical monitor based on the data entered in the eCRF. Subjects may continue ibrutinib treatment until disease progression or meeting the IWCLL criteria for requiring subsequent anti-CLL therapy. For subjects continuing ibrutinib treatment in the main study phase, CT scans should be performed as specified in the Time and Events Schedule titled "After Interim Analysis: Applies to Subjects Continuing Ibrutinib or Subjects in Follow-Up."

should be from as disparate regions of the body as possible. Additional lesions that are present but are not included in the target lesion assessment should be added as non-target lesions and followed throughout the study. The longest diameter of the spleen and liver will be assessed at screening and at all subsequent disease evaluations. All other sites of disease will be considered assessable. Assessable disease includes objective evidence of disease that is identified by radiological imaging, physical examination, or other procedures as necessary including peripheral blood counts.

9.2.1.3. Bone Marrow Assessment[c]

A unilateral bone marrow biopsy must be obtained during screening or up to 90 days before randomization to confirm the diagnosis of CLL or SLL and for morphological evaluation. A bone marrow aspirate or peripheral blood sample should also be obtained within the same timeframe for immunophenotyping (IHC or flow cytometry) and cytogenetics (FISH) to confirm and characterize the diagnosis of CLL or SLL. Conventional karyotype evaluations are optional; FISH is required. For subjects with SLL, a lymph node biopsy may be used for immunophenotyping, morphology, and FISH testing to confirm the diagnosis.

For subjects who have suspected CR based on the most recent physical examination, CT scans, and CBC results, a confirmatory bone marrow aspirate and biopsy must be obtained. This should occur when the subject shows clinical signs of having CR, and should occur no earlier than 2 months following the completion of BR. The bone marrow aspirate and biopsy should be sent to a local laboratory for evaluation of morphology and immunophenotyping. An additional bone marrow aspirate and a concurrent peripheral blood sample will be sent to the central laboratory for MRD analysis. Subsequent follow up for MRD by peripheral blood evaluation will continue every 12 weeks for subjects who obtain a bone marrow evaluation, regardless of the bone marrow biopsy results. As of Amendment INT-4, all responding subjects will be required to have peripheral blood MRD evaluations performed as specified in the Time and Events Schedule "After Interim Analysis: Applies to Subjects Continuing Ibrutinib or Subjects in Follow-Up." After the completion of BR, if there is a new onset of cytopenia, a bone marrow aspirate or biopsy should be performed to determine the underlying cause, ie, autoimmune cytopenias, drug-related cytopenias, or disease progression.

9.2.1.4. Response Categories[d]

Assessment of response should include physical examination, radiographic imaging, and evaluation of blood and bone marrow (if applicable). The definition of response will be

[c] With the implementation of Amendment INT-7, collection of all MRD data is discontinued. The last date for MRD collection is 31 July 2017, which corresponds to approximately 5 years after the first subject entered the study; no further MRD data will be collected after that date.

[d] Following Amendment INT-4, radiographic imaging (ie, CT scans) should be done every 24 weeks, as specified in the Time and Events schedule. Assessment of response should continue to occur every 12 weeks and should include physical examination, and evaluation of blood (local laboratory values) and bone marrow (if applicable). At the visits which do not include a CT scan, radiographic assessments of CLL should be considered together with the evidence of disease status based on physical examinations, evaluations of blood and bone marrow (if applicable).

evaluated by the criteria listed in Table 1 and the text immediately following. Any response must be confirmed by CT and central laboratory values and must last for at least 2 months to be considered confirmed. For response-related definitions, see Attachment 5.

Disease evaluations, for the purpose of the study result analyses, will be performed by an IRC blinded to study treatment information and independent of investigators and personnel who are involved in conduct of the study. As part of the central review, radiographic evaluations will be assessed by an independent radiologist and relevant clinical data will be assessed by an independent oncologist. Detailed procedures will be described in a separate charter.

Table 1 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	

[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 criteria for 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 patients have to lack disease related constitutional symptoms. Bone marrow aspirate at least 2 months following the last dose of bendamustine and rituximab is required to confirm CR.
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).
NOTE: If only 1 measurable Group A criterion is present at baseline (eg, enlarged lymph nodes but no other abnormality), per recent clarification of the IWCLL criteria[46] these subjects are still considered evaluable for PR if the given parameter improves by at least 50% for a minimum of 2 months. 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 2 months 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[22,42,46]

Complete Response with an Incomplete Marrow Recovery (CRi)

CRi is defined as a complete response with an incomplete recovery of the subject's bone marrow. Subjects who have a CRi fulfill the criteria for a CR, but continue to have persistent anemia, thrombocytopenia, or neutropenia, and a hypocellular bone marrow. These cytopenias are due to drug toxicity in the bone marrow and are not due to any evidence of CLL.

Nodular Partial Response (nPR)

nPR is a response where subjects meet the criteria for a CR, but the bone marrow biopsy shows that there are still B-lymphoid nodules present. These nodules are residual disease and therefore the subject is termed an nPR.

Partial Response (PR) with Lymphocytosis

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

Stable Disease

Not meeting criteria for CR, CRi, nPR, PR, 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, hematologic parameters (hemoglobin and platelet count), or disease-related symptoms. Treatment-related lymphocytosis is isolated lymphocytosis occurring when no other criteria for progressive disease are met. In this particular setting, it will not be considered PD. This is supported by the most recent version of the NCCN guidelines and the IWCLL clarification letter.[28,42]

9.2.1.5. Patient-Reported Outcomes[e]

Patient-reported outcomes will be measured by 4 questionnaires. The EORTC QLQ-C30 is a general cancer assessment, the EORTC QLQ-CLL 16 is specific to symptoms or problems associated with CLL, and the FACIT-Fatigue Scale specifically assesses aspects of fatigue. Samples of the PRO scales are provided in Attachments 6, 7, 8, and 9. The PRO questionnaires will be collected preferably at the beginning of the clinic visits prior to any procedures or physician interactions according to the schedule described in the Time and Events Schedules. Data will be collected using electronic data capture to enhance ease of collection and quality of data (fewer missing values and extraneous marks).[35]

[e] With the implementation of Amendment INT-6, collection of all ePRO data is discontinued. The last date for ePRO collection is 18 September 2016, which corresponds to 4 years after the first subject entered the study; no further ePRO data will be collected after that date.

The EORTC QLQ-C30 includes 30 separate items resulting in 5 functional scales (physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning), 1 Global Health Status scale, 3 symptom scales (fatigue, nausea and vomiting, and pain), and 6 single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties).[14] The recall period is 1 week (the past week). The EORTC QLQ-C30 has been widely used among cancer patients in general and specifically in CLL patients.[5,9,25] Scale scores range from 0 to 100. A change of 10 points is considered clinically meaningful for the functioning scales. Administration time is approximately 11 minutes.

The EORTC QLQ-CLL 16 is a 16-item disease specific module that comprises 5 domains of patient-reported health status important in CLL.[12] There are three multi-item scales that include fatigue (2 items), treatment side effects and disease symptoms (8 items), and infection (4 items), and 2 single-item scales on social activities and future health worries. Responses are measured on a 4-point scale ranging from 1 (not at all) to 4 (very much). These scores are transformed to give a rating from 0 (no symptoms or problems) to 100 (severe symptoms or problems). This is a new instrument developed specifically to assess health status of patients with CLL. Item development followed best practices, but the instrument has not been completely validated. Data from this study would contribute to understanding the measurement characteristics and scoring of the instrument in the target population. In addition to scoring the EORTC QLQ-CLL 16 as hypothesized by the instrument developer, other scoring approaches of the instrument may be evaluated. For example, expanding the Disease Effects Scale to include additional items that relate to B-cell or lymphoma symptoms may increase the sensitivity of this domain. The scoring and psychometric validation of the EORTC QLQ-CLL 16 will be examined using blinded treatment group data prior to database lock.

The EQ-5D-5L is a standardized instrument for use as a measure of health outcome.[13] For purposes of this study, the EQ-5D-5L will be used to generate utility scores for use in cost effective analyses. The EQ-5D-5L is a 5-item questionnaire and a "thermometer" visual analog scale ranging from 0 (worst imaginable health state) to 100 (best imaginable health state). The scores for the 5 separate questions are categorical and should not be analyzed as cardinal numbers. However, the scores for the 5 dimensions are used to compute a single utility score ranging from zero (0.0) to 1 (1.0) representing the general health status of the individual. The United Kingdom weights will be used to generate patient utilities from the 5 dimensions of the EQ-5D-5L in this study.

FACIT-Fatigue is an instrument for use as a measure of the effect of fatigue in patients with cancer and other chronic diseases (http://www.facit.org). Responses to the 13-item FACIT-Fatigue Scale are reported on a 5-point categorical response scale ranging from 0 (not at all) to 4 (very much). Higher scores indicate poorer health status. The FACIT-Fatigue Scale has been validated in the general population (http://www.ncbi.nlm.nih.gov/pubmed/11900238) as well as for patients with cancer and rheumatoid arthritis.

9.3. Pharmacokinetics

9.3.1. Evaluations

In both treatment arms, blood samples will be collected from all subjects for determination of plasma concentrations of ibrutinib and the PCI-45227 metabolite (if possible and judged relevant) according to the Time and Events Schedule. These sparse samples will be used for the development of a population-based PK model.

In addition, in a subset of subjects at selected sites, sparse sampling will be performed in both treatment arms according to the Time and Events Schedule to explore a potential effect of ibrutinib on the PK of bendamustine and rituximab. For subjects at the selected sites, participation is mandatory.

9.3.2. Analytical Procedures

Plasma samples will be analyzed to determine either concentrations of ibrutinib and the metabolite PCI-45227 or bendamustine, using a validated, specific, and sensitive LC-MS/MS method by or under the supervision of the sponsor. Serum samples will be analyzed to determine concentrations of rituximab using a validated, specific, and sensitive immune-assay.

9.3.3. Pharmacokinetic Parameters

Population pharmacokinetic analysis of plasma concentration-time data of ibrutinib will be performed using nonlinear mixed-effects modeling (NONMEM), with the aim of providing estimates of PK parameters (eg, oral clearance) or metrics of systemic exposure (eg, area under the plasma concentration-time curve within the dosing interval). Model-derived plasma concentrations or metrics of exposure parameters (eg, Cmax or AUC) may be subjected to further analyses to explore PK correlation between exposure and relevant clinical or biomarker information.

In a subset of subjects at selected sites, population PK of bendamustine and rituximab will also be explored in both arms of the study using NONMEM, with the aim of exploring whether ibrutinib coadministration had an effect on bendamustine and rituximab PK parameters.

9.4. Biomarkers

B-cell receptor signaling is critically involved in the progression of several B-cell malignancies, including CLL/SLL. Bruton's tyrosine kinase is a central regulator of BCR signaling and BCR stimulation leads to its phosphorylation and subsequent activation. Ibrutinib, an irreversible inhibitor of BTK, induces apoptosis and inhibits cellular migration and adhesion in malignant B cells.

To better understand the mechanism of action of ibrutinib with an aim to develop predictors of resistance, blood samples will be collected as specified in the Time and Events Schedules and analyzed. Results will be used to inform development in other B-cell indications.

Plasma protein analysis may evaluate potential serum protein biomarkers that may contribute to BTK resistance or sensitivity. Isolated peripheral B-lymphocytes may also be evaluated for 1) protein expression of ZAP-70, CD38, 2) RNA/DNA status for IgVH (mut/non-mut), and 3) other RNA/DNA signatures that may predict acquired resistance.

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.

9.4.1. Circulating B-lymphocytes From Blood

B-lymphocytes may be isolated from collected samples and may be characterized for gene expression profiling (GEP) somatic mutation analysis (SMA) and protein expression of ZAP-70, CD38 as well as other potential biomarkers that may contribute to resistance to BTK inhibition in CLL. Absolute lymphocyte counts will be determined for each subject at each collection timepoint, and samples will be subjected to designated analyses. Plasma protein analysis may include evaluation of interleukin (IL)-4, IL-6, and CXCL-12, as well as other potential serum protein biomarkers that may contribute to BTK resistance or sensitivity.

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 will be followed by the investigator until resolution or until a clinically stable endpoint is reached or until the end of the study.

Adverse Events

All AEs, with the exception of progression of CLL/SLL, will be reported from the time a signed and dated informed consent form is obtained until 30 days following the last dose of study treatment or until the start of a subsequent systemic antineoplastic 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. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol. Adverse events will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally-acceptable representative) for the duration of the study. Adverse events will be followed by the investigator as specified in Section 12, Adverse Event Reporting. Non-hematologic AEs and hematologic AEs events will be graded according to specifications listed in Section 12.1.3.

For subjects who crossover to next-line ibrutinib treatment, all AEs from the time a signed and dated informed consent form for crossover is obtained until 30 days following the last dose of study drug will be reported.

Clinical Laboratory Tests

CBCs obtained as per the Time and Events Schedule will be sent to a central laboratory to perform the assay. Other tests should be performed at the laboratory facilities associated with the investigational site, 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 has the laboratory assessments conducted at a laboratory 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 Schedule. The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the adverse event section of the CRF. For example, laboratory abnormalities leading to an action regarding study treatment (dose change, temporary stop, delay of the start of a cycle, or permanent stop) 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 CRF: 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.

Refer to Section 8.1 for risk factors and management of subjects considered to be at risk of TLS.

The following tests will be performed:

- Hematology Panel (central laboratory)
  -hemoglobin -ANC
  -WBC count -ALC
  -platelet count

- Serum Chemistry Panel (local laboratory)
  -lactic acid dehydrogenase (LDH) -ALT
  -creatinine -total bilirubin
  -potassium -direct bilirubin (optional when total bilirubin is within normal limits)
  -alkaline phosphatase -albumin
  -AST -uric acid
  -phosphate -sodium
  -magnesium

- Coagulation (local laboratory)
  -activated partial thromboplastin time (aPTT)
  -INR
- Hepatitis B Screening (local laboratory)
  -Hepatitis B surface antigen -Hepatitis B core antibody

Hepatitis B DNA needs to be performed if Hepatitis B Core Antibody is positive. DNA PCR needs to be confirmed negative prior to randomization in subjects who are Hepatitis B core Ab positive. During study treatment and for at least 12 months following the last dose of rituximab, regular monitoring of Hepatitis B PCR and liver enzymes and prophylactic antiviral medication should be considered per published guidelines.[44]

- Hepatitis C Screening (local laboratory)

  -Hepatitis C antibody
- Urine or serum β-hCG pregnancy testing for women of childbearing potential only (local laboratory)
- Beta2-microglobulin and serum immunoglobulin levels (IgG, IgM, IgA) (local laboratory)
- If additional laboratory parameters (eg, absolute reticulocyte counts, Coombs tests, blood urea nitrogen, calcium, glucose, total protein, chloride, creatine phosphokinase, haptoglobin) are obtained because of an adverse event, they should be documented at an unscheduled visit (local laboratory).

After interim analysis, the following clinical laboratory tests will be performed by the local laboratory, as specified in the Time and Events schedule:

- Hematology Panel

  -hemoglobin -ANC
  -WBC count -ALC
  -platelet count

- Serum Chemistry Panel

  -potassium -AST
  -creatinine -ALT
  -total bilirubin
  -alkaline phosphatase

Vital Signs

Temperature, heart rate, and blood pressure will be recorded at screening. Blood pressure and heart rate measurements should be preceded by at least 5 minutes of rest in a quiet setting without distractions (eg, television, cell phones).

Body Surface Area

Calculation of body surface area (BSA) at Cycle 1, Day 1 is required for bendamustine hydrochloride and rituximab dosing. The IWRS will collect the height and weight of the subject at randomization and calculate the BSA. The IWRS will collect the weight at each subsequent cycle. If there is a >10% change in weight from the weight used in the most recent BSA calculation, the IWRS will re-calculate the BSA and adjust the dose accordingly. Weight will be collected as specified in the Time and Events Schedule.

Physical Examination

A complete physical examination will be conducted at screening. During treatment cycles, a limited focused physical examination must be must be performed to document the presence or absence, increase or decrease or no change in the status of lymph nodes, liver, and spleen. During the examination, review of symptoms should include inquiry of ocular symptoms (eg, dry eye, watering eye/abnormal discharge, eye pain, blurred vision/double vision, decreased visual acuity, photophobia/sensitivity to light, floaters, flashing lights, and eye irritation). Subjects should be referred to an ophthalmologist for a formal examination if any Grade ≥2 symptoms are reported.

Electrocardiograms

An ECG will be performed at screening for all subjects. For a subset of subjects at selected sites, additional ECGs will be performed according to the Time and Events Schedule. The subject should be in a quiet setting without distractions (eg, television, cell phones). Subjects should rest in a supine position for at least 5 minutes before ECG collection and should refrain from talking or moving arms or legs. Abnormalities noted at screening should be included in the medical history.

9.6. Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the CRF or laboratory requisition form. Refer to the Time and Events Schedule for the timing and frequency of all sample collections. Instructions for the collection, handling, and shipment of samples are found in the laboratory manual that will be provided for sample collection and handling.

10. SUBJECT COMPLETION/WITHDRAWAL

10.1. Completion

A subject will be considered to have completed the study if he or she has died before the end of the study, has not been lost to follow up, or has not withdrawn consent before the end of study.

10.2. Discontinuation of Treatment

If a subject's study treatment must be discontinued, then this will 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 Schedule. A subject's study treatment should 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, adverse event) 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 determined to have disease progression and provide documentation of disease progression for review by the sponsor’s 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 CT scan.

10.3. Withdrawal From the Study

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

- Lost to follow-up
- Withdrawal of consent
- The sponsor discontinues the 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/withdrawal. The measures taken to follow up must be documented.

When a subject withdraws before completing the study, the reason for withdrawal is to be documented in the CRF and in the source document. Study drug assigned to the withdrawn subject may not be assigned to another subject. Subjects who withdraw will not be replaced.

Withdrawal From the Use of Samples in Future Research

The subject may withdraw consent for use of samples for research (refer to Section 16.2.5, Long-Term Retention of Samples for Additional Future Research). In such a case, samples will be destroyed after they are no longer needed for the clinical study. Details of the sample retention for research are presented in the main Informed Consent Form (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.

11.1. Analysis Sets

The intent-to-treat (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 primary efficacy analyses including PFS 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 subjects actually received. The PK evaluable population will include all subjects who receive at least 1 dose of study medication and have at least 1 post-treatment PK sample.

11.2. Sample Size Determination

A recent Phase 2 study reported a median PFS of 15 months in patients with relapsed or refractory CLL treated with combination of BR.[15] It is assumed that the PFS follows an exponential distribution with a constant hazard ratio.

Approximately 580 subjects (290 per treatment group) will be randomized to observe 342 PFS events. The study is designed to detect a hazard ratio of 0.7 for the ibrutinib + BR group relative to placebo + BR group (corresponding to an improvement of 43% in median PFS, eg, from 15 months to 21.5 months) with 90% power at a 1-sided significance level of 0.025, using a group sequential testing design. Assuming the enrollment rate is on average 32 subjects per month, the total study duration is expected to be approximately 33 months with 18 months of enrollment and 15 months of follow up in order to observe 342 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, height, weight, blood pressure, and BSA. Baseline disease characteristics (documented in the source documents and CRF) will include time from initial diagnosis to randomization, histological diagnosis (CLL, SLL), stage of disease, treatment history (relapsed, refractory), and ECOG Performance Score (0, 1).

11.4. Efficacy Analyses

11.4.1. Primary Efficacy Endpoint

The primary efficacy endpoint, PFS, is defined as the interval between the date of randomization and the date of disease progression or death, whichever is first reported. Disease progression will be based on assessments from an IRC, using 2008 IWCLL Guidelines as defined in Section 9.2.1.4. The process and conventions of the IRC will be detailed in a separate IRC charter.

All subjects, including those who discontinued study treatment or started new antineoplastic therapy, will be followed for PFS until a PFS event occurs (disease progression or death) or until the data cutoff. For subjects who receive subsequent antineoplastic therapy without documented progression, data will be censored at the date of the last disease evaluation before the start of such therapy. For subjects who have not progressed and are still alive at the cutoff date for the final analysis or who withdraw from the study (withdrawal of consent or lost to follow up), data will be censored at the date of the last disease evaluation.

After interim analysis, PFS and overall survival will be updated at subsequent analyses.

11.4.2. Secondary Efficacy Endpoints

The secondary efficacy endpoints are as follows:

- ORR, defined as the proportion of subjects with measurable disease achieving a best overall response of either CR, CRi, PR, or nPR, as evaluated by the IRC
- OS, defined as the interval between the date of randomization and the date of death from any cause. Survival time of living subjects will be censored on the last date a subject is known to be alive or lost to follow-up.
- Rate of MRD-negative remissions, defined as the proportion of subjects who reach MRD-negative disease status (<1 CLL cell per 10,000 leukocytes)

- Improvement in disease-related symptoms (fatigue, night sweats, weight loss, fever, and abdominal discomfort due to splenomegaly)
- Hematologic improvement in the subset of subjects with cytopenia(s) at baseline (hemoglobin <11 g/dL, platelets <100 x 10^9/L [ie, <100,000/µL], or ANC <1.5 x 10^9/L [ie, <1500/µL]), with sustained improvement defined as improvement in cytopenias by ≥50%, or hemoglobin ≥11 g/dL, ANC ≥1.5 x 10^9/L (ie, ≥1500/µL), platelets ≥100 x 10^9/L (ie, ≥100,000/µL), with the duration of improvement lasting for ≥60 days without blood transfusion or growth factors.
- Improvement in patient-reported symptoms, functional status, and well-being as measured by:
  - The FACIT-Fatigue Scale summary score
  - The EORTC QLQ-C30 Physical Functioning Score
  - The EORTC QLQ-CLL 16 domain scores

11.4.3. Analysis Methods

The primary efficacy analysis will be based on the PFS determined by the IRC and will be performed on the ITT population, which is defined as all randomized subjects. 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 the PFS between the 2 treatment groups. The median PFS will be provided for each treatment group and the hazard ratio for ibrutinib + BR relative to placebo + BR and its associated 95% confidence interval (CI) will be calculated based on the Cox proportional hazards model stratified by the stratification factors. Investigator-determined PFS will be analyzed as a sensitivity analysis of primary efficacy analysis.

For the secondary efficacy endpoints, OS will be compared using the stratified log-rank test. The Kaplan-Meier method will be used to estimate the distribution of OS for each treatment group. The ORR and the rate of MRD-negative remissions will be obtained and comparison of the rates will be performed between the 2 treatment groups using the Cochran-Mantel-Haenszel chi-square test. Disease-related symptom improvement and hematologic improvement data will be summarized as appropriate. Scores from EORTC QLQ-C30, EORTC QLQ-CLL 16, EQ-5D-5L, and the FACIT-Fatigue will be descriptively summarized by treatment group. Longitudinal analysis with repeated measures may be used as appropriate. Multiplicity adjustment will be made for analyses of selected secondary efficacy endpoints to control the overall type 1 error. Details will be specified in the statistical analysis plan.

11.5. Pharmacokinetic Analyses

The plasma concentration data for ibrutinib and, if possible and judged relevant, PCI-45227 at each timepoint will be summarized using descriptive statistics.

Population PK analysis of ibrutinib plasma concentration-time data will be performed using NONMEM. Data may be combined with data from other studies to support a relevant structural

population-based PK model. Available subject characteristics (demographics, laboratory variables, genotypes, etc.) will be tested as potential covariates affecting PK parameters.

Ibrutinib data will be listed for all subjects with available plasma concentrations per treatment group. Subjects will be excluded from the PK analysis if their data do not allow for accurate assessment of the PK (eg, incomplete administration of the study agent; concentration data not sufficient for PK parameter calculation due to missing PK draws at multiple visits; or early discontinuation from the study).

All concentrations below the lowest quantifiable concentration or missing data will be labeled as such in the concentration data presentation. Concentrations below the lowest quantifiable concentration will be treated as zero in the summary statistics and for the calculation of PK parameters. All subjects and samples excluded from the analysis will be clearly documented in the study report.

Model-derived exposure parameters may be subjected to further explore PK/pharmacodynamic correlation between exposure with relevant clinical or biomarker information.

The plasma concentration data for bendamustine and rituximab at each timepoint will be summarized using descriptive statistics. Population PK analysis of plasma concentration-time data will be performed using NONMEM. Pharmacokinetic parameters will be obtained from population PK models reported in the literature with the aim of exploring whether ibrutinib coadministration had an effect on bendamustine and rituximab PK parameters.[29,35]

Details of the analyses will be given in a population PK analysis plan and the results of the population PK analyses will be presented in a separate report.

11.6. Biomarker Analyses

Biomarker studies are designed to identify markers predictive of resistance to ibrutinib. 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 [ANOVA], categorical, or survival model), depending on the endpoint. Results may be presented in a separate report.

11.7. Safety Analyses

Analysis of safety data will be conducted on the safety population, which includes subjects randomized who receive any study treatment. All data will be analyzed according to the treatment actually received.

The safety variables to be analyzed include AEs, clinical laboratory tests (hematology and chemistry), physical examination results, ECGs, and deaths. 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 CRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). All reported AEs with onset during the treatment phase (ie, treatment-emergent AEs, 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 adverse events of special interest may be counted or listed. Adverse events of special interest will be summarized similarly to treatment-emergent adverse events.

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.

11.8. Interim Analysis

An interim analysis using classical O'Brien & Fleming boundary for both efficacy and futility will be conducted after observing approximately 50% (171) PFS events (PD or death).[29] The stopping boundaries were implemented by Lan-Demets spending function using East® software v5.3 to control the 1-sided Type I error of 0.025 and Type II error of 0.10 for the comparison on PFS endpoint. This method ensures that the type I error is not inflated. The 1-sided cumulative alpha spent will be 0.0015 at the interim and 0.025 at the final analysis. Assuming the enrollment rate is 32 subjects per month, the interim analysis will take place after approximately 19 months after the first subject has been randomized. The exact timing of the interim analysis will be determined according to the PFS events required.

The DMC may make recommendations regarding study continuation if the pre-specified boundary is crossed for efficacy or futility.

11.9. Data Monitoring Committee

An independent DMC will be formed to monitor data on a regular basis to ensure the safety of the subjects in this study, assess the evidence of benefit or adverse effects of ibrutinib, and to monitor the conduct of the study. The DMC is comprised of experts in CLL/SLL, medical safety, and biostatistical aspects of clinical studies. Details regarding DMC roles, responsibilities, and activities will be provided in a separate DMC Charter.

At the interim analysis, the DMC may make recommendations regarding study continuation if the pre-specified stopping boundary is crossed for efficacy or futility. In addition to the planned interim analysis, the DMC will meet periodically to review the cumulative safety data throughout the study. There will be 2 planned safety review meetings. The first safety review meeting will be held after approximately 120 subjects (~20% of the expected enrollment) have been randomized, and the second will be after approximately 300 subjects have been randomized. The DMC safety review will focus on deaths, treatment discontinuations, SAEs, and Grade 3/4 AEs and AEs of special interest, to identify any potential added toxicity when ibrutinib is combined with BR. Based on the results from these scheduled safety review meetings, the DMC chair may request additional safety analyses and more frequent monitoring. Until the first safety review, all deaths, treatment discontinuations, and SAEs will be reviewed by the sponsor's responsible physician on an ongoing basis to identify safety concerns, and the DMC will be informed of any new potential signals.

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 adverse event is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the treatment. An adverse event 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 adverse events starting with the signing of the informed consent form (refer to Section 12.3.1, All Adverse Events, for time of last adverse event recording).

Serious Adverse Event

A serious adverse event 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 adverse event is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For an investigational product, the expectedness of an adverse event will be determined by whether or not it is listed in the Investigator's Brochure. For a non-sponsor investigational medicinal product (eg, a comparator product) with a marketing authorization, the expectedness of an adverse event will be determined by whether or not it is listed in the Treanda USPI[40] or the Rituxan USPI[41].

Adverse Event Associated With the Use of the Study Treatment

An adverse event 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 adverse event that is not related to the use of the treatment.

Doubtful

An adverse event 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 adverse event that might be due to the use of the treatment. 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 adverse event that might be due to the use of the treatment. 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 adverse event 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 adverse event. The severity assessment for a non-hematologic adverse event or serious adverse event should be completed using the NCI CTCAE Version 4.03. Any non-hematologic adverse event or serious adverse event not listed in the NCI CTCAE Version 4.03 will be graded according to investigator clinical judgment by using the standard grades as follows:

Grade 1: Mild AE

Grade 2: Moderate AE

Grade 3: Severe AE

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

An evaluation of hematologic toxicity in subjects with advanced CLL/SLL must consider the high frequency of marrow involvement and previous exposure to chemotherapy with consequent medullary compromise at the initiation of therapy. The standard hematologic grading system for solid tumors cannot, therefore, be directly applied. A substantial proportion of subjects would be

considered to have Grade 2 to 4 hematologic toxicity before any therapy is given. Therefore, the following modified schema will be used to quantitate hematologic deterioration, in accordance with the IWCLL recommendations.[22]

Table 2 Hematologic Adverse Event Grading Table

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 pretreatment, in which case the patient 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 patient is not evaluable for toxicity referable to the ANC.

Reference: Hallek 2008[22]

12.2. Special Reporting Situations

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

- Overdose of a sponsor medicinal product
- Suspected abuse/misuse of a sponsor medicinal product
- Inadvertent or accidental exposure to a sponsor medicinal product
- Medication error involving a sponsor product (with or without subject/patient exposure to the sponsor medicinal product, eg, name confusion)

Special reporting situations should be recorded in the CRF. Any special reporting situation that meets the criteria of a serious adverse event should be recorded on the serious adverse event page of the CRF.

12.3. Procedures

12.3.1. All Adverse Events

All subjects who receive treatment will be considered evaluable for toxicity. All adverse events (with the exception of progression of CLL) and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated informed consent form is obtained until 30 days following the last dose of study treatment or until the start of a subsequent systemic antineoplastic 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 drug must be followed until recovery to Grade ≤1. The unresolved aforementioned events

will be followed for a maximum of 6 months. All AEs related to bleeding or resulting in bleeding complications must be followed until recovery to Grade ≤1. In addition to all 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 overall survival.

Serious adverse events, 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. Progressive disease of CLL (for which there are protocol-specific assessments), should NOT be reported as an AE, but instead symptoms/clinical signs of unexpected disease progression are to be reported. Otherwise, all events that meet the definition of a serious adverse event will be reported as serious adverse events, regardless of whether they are protocol-specific assessments.

All adverse events, regardless of seriousness, severity, or presumed relationship to study therapy, must be recorded using medical terminology in the source document and the CRF. 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 CRF their opinion concerning the relationship of the adverse event to study therapy. All measures required for adverse event 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 adverse events to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all serious adverse events 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:

- Subject's name
- Subject number
- Study site number
- Investigator's name and 24-hour contact information
- Local sponsor's name and 24-hour contact information

- Statement that the subject is participating in a clinical study.

12.3.2. Serious Adverse Events

All serious adverse events occurring during clinical studies must be reported to the appropriate sponsor contact person by investigational staff within 24 hours of their knowledge of the event.

Information regarding serious adverse events will be transmitted to the sponsor using the Serious Adverse Event Form, which must be completed and signed by a member of the investigational staff, and transmitted to the sponsor within 24 hours. The initial and follow-up reports of a serious adverse event should be made by facsimile (fax) or may be made by telephone report in exceptional circumstances.

All serious adverse events 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 drug 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 a serious adverse event. Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a subject's participation in a clinical study must be reported as a serious adverse event, except hospitalizations for the following:

- A standard procedure for protocol therapy administration, including administration of background therapy (BR), 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, pharmacokinetic or 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 adverse event

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

Disease progression should not be recorded as an adverse event or serious adverse event term; instead, signs and symptoms of clinical sequelae resulting from disease progression/lack of efficacy will be reported if they fulfill the serious adverse event definition (see Section 12.1.1, Adverse Event Definitions and Classifications).

12.3.3. Adverse Events of Interest

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

12.3.3.1. Major Hemorrhage

Major hemorrhage is defined as:

- Any treatment-emergent hemorrhagic adverse event of Grade 3 or higher. All hemorrhagic events requiring a transfusion of red blood cells should be reported as Grade 3 or higher adverse events per NCI CTCAE.

- Any treatment-emergent serious adverse event of bleeding of any grade.

- Any treatment-emergent central nervous system hemorrhage/hematoma of any grade.

12.3.4. Pregnancy

All initial reports of pregnancy 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, stillbirth, and congenital anomaly) are considered serious adverse events and must be reported using the Serious Adverse Event Form. Any subject who becomes pregnant during the study must discontinue further study treatment.

The effect of the study drug 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.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

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 on 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. PQCs may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC 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 procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information; all clinical 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 investigational staff within 24 hours after being made aware of the event.

If the defect is combined with a serious adverse event, then the investigational staff must report the PQC to the sponsor according to the serious adverse event 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 on the Contact Information page(s), which will be provided as a separate document.

14. STUDY DRUG INFORMATION

14.1. Physical Description of Study Drug(s)

Ibrutinib capsules are provided as a hard gelatin capsule containing 140 mg of ibrutinib. All formulation excipients are compendial and are commonly used in oral formulations. Refer to the ibrutinib Investigator's Brochure for a list of excipients.

Placebo to match capsules will also be provided as a hard gelatin capsule.

Bendamustine hydrochloride may be provided in 100-mg single-use vials as a lyophilized powder or prescribed by the investigator. Rituximab may be provided in 100-mg or 500-mg single use vials as a solution or prescribed by the treating physician.

14.2. Packaging

To maintain the blind, the ibrutinib capsules and placebo to match capsules are packaged in opaque high-density polyethylene (HDPE) plastic bottles with labels bearing the appropriate label text as required by governing regulatory agencies. All bottles will utilize child resistant packaging (caps will be child resistant).

14.3. Labeling

Study drug labels will contain information to meet the applicable regulatory requirements. Each bottle will contain a study specific label with a unique identification number.

Study drug 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 to 25°C). Current stability data indicate that the capsules will be stable for the duration of the clinical study under the labeled storage conditions. Refer to the Site Investigational Product Procedures Manual for additional guidance on study drug preparation and handling.

14.5. Drug Accountability

The investigator is responsible for ensuring that all study drug received at the site is inventoried and accounted for throughout the study. The dispensing of study drug to the subject, and the return of study drug 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 drug. All study drug will be stored and disposed of according to the sponsor's instructions. Site staff must not combine contents of the study drug containers.

Study drug 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 drug, and study drug 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 study drug, or used returned study drug for destruction, will be documented on the drug return form. When the site is an authorized destruction unit and study drug 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 drug should be dispensed under the supervision of the investigator or a qualified member of the investigational staff, or by a hospital/clinic pharmacist. Study drug will be supplied only to subjects participating in the study. Returned study drug must not be dispensed again, even to the same subject. Study drug may not be relabeled or reassigned for use by other subjects. The investigator agrees neither to dispense the study drug from, nor store it at, any site other than the study sites agreed upon with the sponsor.

Details of the background therapy (BR) dispensed must be recorded on a drug accountability form. Handling and disposal of BR must be performed according to the appropriate labeling instructions and institution guidelines.

15. STUDY-SPECIFIC MATERIALS

The investigator will be provided with the following supplies:

- Study Protocol
- Subject study tools (appointment card, emergency ID card etc, as applicable per country)
- Investigator study tools and quick reference cards
- Ibrutinib Investigator's Brochure
- Package inserts for bendamustine hydrochloride and rituximab
- Trial Center File, and corresponding site specific documentation
- Site Investigational Product Procedures manual and Site IP Binder
- Laboratory manual and laboratory kits
- Notification procedure for subject disease progression
- 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, EORTC QLQ-CLL 16, 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 Attachments 6, 7, 8, and 9, but should not be used for collection of subject data.
- IWRS Manual and codes
- eDC Manual and electronic CRF Completion Guidelines

16. ETHICAL ASPECTS

16.1. Study-Specific Design Considerations

In addition to receiving either ibrutinib or placebo, all subjects will receive active treatment with BR as background therapy, which is recommended treatment by NCCN and ESMO for the patient population in this study. All participating subjects will receive full 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 will occur through regular clinic visits including laboratory analyses.

Potential subjects will be fully informed of the risks and requirements of the study and, during the study, subjects will be given any new information that may affect their decision to continue participation. They will be told 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 adverse events of the study, and provide their consent voluntarily will be enrolled.

The total blood volume to be collected is estimated at 335 mL for the first year, 25 mL every 12 weeks following the first year, and 32 mL at the end-of-treatment visit. For a subset of subjects at selected sites, an additional 40 mL of blood will be drawn in the first year to explore the potential effect of ibrutinib on bendamustine and rituximab PK. This includes laboratory assessments associated with treatment and includes pharmacokinetic and biomarker samples. 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 clinical 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 clinical 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:

- Final protocol and, if applicable, amendments
- Sponsor-approved informed consent form (and any other written materials to be provided to the subjects)
- Investigator's Brochure (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 given full approval of the final protocol, amendments (if any), the informed consent form, 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
- Revision(s) to informed consent form 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 Investigator's Brochure and amendments/addenda
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of adverse events that are serious, unlisted/unexpected, and associated with the investigational drug. From Amendment INT-4, these will no longer be provided for bendamustine or rituximab.
- 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 informed consent form 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 clinical study. The reapproval should be documented in writing (excluding the ones that are purely administrative, with no consequences for subjects, data, or study conduct).

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 consent form must be signed before performance of any

study-related activity. The consent form 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 informed consent 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 investigational staff 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 informed consent form 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 informed consent form and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of either the subject's personally dated signature. After having obtained the consent, a copy of the informed consent form must be given to the subject.

If the subject is unable to read or write, then 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 informed consent form 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 study subjects confidential.

The informed consent obtained from the subject includes explicit consent for the processing of personal data and for the investigator to allow direct access to his or her original medical records

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.

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

Samples collected in this study may be stored for up to 2 years (or according to local regulations) for additional research. Samples will only be used to understand ibrutinib, to understand CLL/SLL, to understand differential drug responders, and to develop tests/assays related to ibrutinib and CLL/SLL. 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 10.3, Withdrawal From the Study).

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, unless explicitly addressed as a specific ethical consideration in Section 16.1, Study-Specific Design Considerations.

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 or its designee. When the change(s) involves only logistic or administrative aspects of the study, the IRB (and IEC 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 (see Contact Information page(s) provided separately). 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 CRF 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 drug to the investigational site:

- Protocol and amendment(s), if any, signed and dated by the principal investigator
- A copy of the dated and signed, written IEC/IRB approval of the protocol, amendments, informed consent form, 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 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, then a general statement may be substituted for this list. If an investigator or a member of the investigational staff is a member of the IEC/IRB, then 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)
- 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 clinical subinvestigators
- Documentation of subinvestigator 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 number and date of birth. In cases where the subject is not randomized into the study, the date seen and date of birth 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 documentation must be available for the following to confirm data collected in the CRF: subject identification, eligibility, and study identification; study discussion and date of informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all adverse events and follow-up of adverse events; concomitant medication; drug receipt/dispensing/return records; study drug administration information; and date of study completion and reason for early discontinuation of study drug or withdrawal from the study, if applicable.

In addition, 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 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.

17.5. Case Report Form Completion

Case report forms are provided for each subject in electronic format.

Electronic Data Capture (eDC) will be used for this study. The study data will be transcribed by study personnel from the source documents onto an electronic CRF, 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 CRF.

Worksheets may be used for the capture of some data to facilitate completion of the CRF. Any such worksheets will become part of the subject's source documentation. All data relating to the study must be recorded in CRFs prepared by the sponsor. Data must be entered into CRFs in English. Designated site personnel must complete the CRF as soon as possible after a subject visit, and the forms should be available for review at the next scheduled monitoring visit. The investigator must confirm that all data entries in the CRFs are accurate and correct.

All CRF entries, corrections, and alterations must be made by the investigator or other authorized study-site personnel. If necessary, queries will be generated in the eDC tool. The investigator or an authorized member of the investigational staff must adjust the CRF (if applicable) and complete the query.

If corrections to a CRF are needed after the initial entry into the CRF, then this can be done in 3 different ways:

- 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 can generate a query for resolution by the investigational staff
- Clinical data manager can generate a query for resolution by the investigational staff

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, and 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 CRF completion will be provided and reviewed with study personnel before the start of the study.

The sponsor will review CRFs 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 CRFs 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, then 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, then the investigator must permit access to such reports.

17.8. Monitoring

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 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 CRFs with the hospital or clinic records (source documents). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the CRF are known to the sponsor and investigational staff and are accessible for verification by the sponsor site contact. If electronic records are maintained at the investigational site, then the method of verification must be discussed with the investigational staff.

Direct access to source documentation (medical records) must be allowed for the purpose of verifying that the data recorded in the CRF are consistent with the original source data. Findings from this review of CRFs and source documents will be discussed with the investigational staff. The sponsor expects that, during monitoring visits, the relevant investigational staff will be available, the source documentation 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.

17.9. Study Completion/Termination

17.9.1. Study Completion

The study is considered completed when 80% of the subjects have died or 5 years after the last subject is randomized into the study, whichever occurs first. The sponsor will ensure that subjects benefiting from treatment with ibrutinib will be able to continue treatment after the end of the study. The final data from the investigational site will be sent to the sponsor (or designee)

after completion of the final subject assessment at that site, in the time frame specified in the Clinical Trial Agreement.

17.9.2. Study Termination

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

The investigator may initiate 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 an investigational 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 drug development

17.10. On-Site Audits

Representatives of the sponsor's clinical quality assurance department may visit the 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 and comparison with the CRFs. Subject privacy must, however, be respected. The investigator and staff are responsible for being present and available for consultation during routinely scheduled 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/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 clinical 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 CRF data from all investigational sites that participated in the study, and direct transmission of clinical laboratory data from a central laboratory, and electronic PRO data into the sponsor's data base. 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. Results of 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 biomarker 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, then 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 site until the combined results from the completed study have been submitted for publication, within 12 months of the availability of the final data (tables, listings, graphs), 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 Uniform Requirements for Manuscripts Submitted to Biomedical Journals, which state that the named authors must have made a significant contribution to the design of the study or analysis and interpretation of the data, provided critical review of the paper, and given final approval of the final version.

Registration of Clinical Studies and Disclosure of Results

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

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Attachment 1: Eastern Cooperative Oncology Group Performance Status Scale

Grade	Eastern Cooperative Oncology Group Performance Status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair[33]

Attachment 2: 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 three 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 three 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 two 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 3: Inhibitors and inducers of CYP3A4/5

Examples of inhibitors and inducers of CYP3A4/5 can be found at the following website: http://medicine.iupui.edu/clinpharm/ddis/table.aspx.[43] The list below reflects information obtained from the Indiana University, Division of Clinical Pharmacology, Indianapolis, IN website on July 2013.

- A strong inhibitor is one that causes a >5-fold increase in plasma AUC values or >80% decrease in clearance. Strong inhibitors are capitalized in the list below.
- A moderate inhibitor is one that causes a >2-fold increase in plasma AUC values or 50-80% decrease in clearance.
- A weak inhibitor is one that causes a >1.25-fold but <2-fold increase in plasma AUC values or 20-50% decrease in clearance.

Inhibitors of CYP3A4/5

Strong inhibitors:	**All other inhibitors:**
INDINAVIR	amiodarone
NELFINAVIR	NOT azithromycin[a]
RITONAVIR	chloramphenicol
CLARITHROMYCIN	boceprevir
ITRACONAZOLE	ciprofloxacin
KETOCONAZOLE	delaviridine
NEFAZODONE	diethyl-dithiocarbamate
SAQUINAVIR	fluoxetine-metabolite norfluoxetine
TELTHROMYCIN	fluvoxamine
Moderate inhibitors:	gestodene
aprepitant	imatinib
erythromycin	mibefradil
diltiazem	mifepristone
fluconazole	norfloxacin
grapefruit juice	norfluoxetine
Seville orange juice	star fruit
verapamil	telaprevir
Weak inhibitors:	troleandomycin
cimetidine	voriconazole

[a] Azithromycin is unique in that it does not inhibit CYP3A4.

Inducers of CYP3A4/5

efavirenz	phenobarbital
nevirapine	phenytoin
barbiturates	pioglitazone
carbamazepine	rifabutin
glucocorticoids	rifampin
modafinil	St. John's wort
oxcarbazepine	troglitazone

Attachment 4: Maximum Blood Volumes During the Study

Maximum Volume of Blood to be Collected From Each Subject

Type of Sample	Volume per Sample (mL)	No. of Samples per Subject (First Year)	Total Volume of Blood (mL)[a] (First Year)	No. of Samples (q 12 weeks after First Year)	Total Volume of Blood (mL)[a] (q 12 weeks after First Year	No. of Samples End-of Treatment Visit	Total Volume of Blood (mL)[a] End-of Treatment Visit
Serum chemistry[c]	5	16	80	1	5	1	5
Serum β-hCG pregnancy test	2	1	2	0	0	0	0
Serology (Hepatitis)	5	1	5	0	0	0	0
Coagulation	2	1	2	0	0	0	0
Hematology[c]	5	21	105	2[b]	10[b]	1	5
CLL diagnosis	20	1	20	0	0	0	0
Pharmacokinetic samples	2	8	16	0	0	0	0
Serum immunoglobulin	5	5	25	1	5	1	5
Minimum residual disease	10	2	20	1	10	0	0
Biomarkers[c]	17	3	51	0	0	1	17
Biomarker analyses (ZAP-70, CD38, IgVH)	9	1	9	0	0	0	0
TOTAL			335		25		32
Additional PK samples (subset of subjects only)	2	20	40	0	0	0	0

a. Calculated as number of samples multiplied by amount of blood per sample. Blood volume for CLL diagnosis may vary by country or site, where additional blood may be drawn to be sent to a separate local laboratory.
b. Only 1 sample (5 mL) would be taken if the every-12-week disease assessment occurs at the same time as the every-3-cycle assessment.
c. For subjects receiving ibrutinib treatment: Only 1 sample (5 mL) will be taken at screening for serum chemistry evaluations; and 2 samples (17 mL each) will be taken for biomarker samples. Blood samples for CBC evaluations will be collected at screening, on Day 1 of Treatment Phase and at weeks 2, 4, 8, and 12 and then every 12 weeks thereafter until progression, and at the end of treatment visit. Each CBC sample is 5 mL.

Attachment 5: Response-related Definitions

Minimal Residual Disease

MRD is determined by flow cytometry. MRD negative is defined as <1 CLL cell per 10,000 leukocytes.[2] This should be performed on the bone marrow aspirate when available. Peripheral blood MRD testing can also be performed by flow cytometry in those subjects that achieve a CR.

Sustained Hematologic Improvement

In the subset of patients with cytopenia(s) at baseline (hemoglobin <11 g/dL, platelets <100 x 10^9/L [ie, <100,000/μL], or ANC <1.5 x 10^9/L [ie, <1500/μL]), a sustained improvement is defined as an improvement in cytopenias by >50% from baseline, or hemoglobin ≥11 g/dL, ANC ≥1.5 x 10^9/L (ie, ≥1500/μL), platelets ≥100 x 10^9/L (ie, ≥100,000/μL) with the duration of improvement lasting for ≥60 days without blood transfusion or growth factors.

Richter's Transformation

Richter's transformation is characterized by the development of high-grade NHL or Hodgkin's disease. This can include new or progressive lymphadenopathy or organomegaly, fever, loss of weight and muscle mass, and other health problems. Confirmation of Richter's transformation is made with a biopsy (eg, lymph node) demonstrating the histologic transformation.

Attachment 6: 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 7: EORTC QLQ-CLL 16

EORTC QLQ – CLL16

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:	Not at All	A Little	Quite a Bit	Very Much
31. Have you lost weight?	1	2	3	4
32. Have you had a dry mouth?	1	2	3	4
33. Did you bruise?	1	2	3	4
34. Did you have abdominal discomfort?	1	2	3	4
35. Has your temperature been going up and down?	1	2	3	4
36. Did you have night sweats?	1	2	3	4
37. Have you had skin problems (e.g. itchy, dry)?	1	2	3	4
38. Did you feel ill or unwell?	1	2	3	4
39. Did you feel lethargic?	1	2	3	4
40. Have you felt "slowed down"?	1	2	3	4
41. Were you limited in planning activities, for example meeting friends, in advance?	1	2	3	4
42. Were you worried about your health in the future?	1	2	3	4

During the past four weeks:	Not at All	A Little	Quite a Bit	Very Much
43. Have you had trouble with chest infections?	1	2	3	4
44. Have you had trouble with other infections?	1	2	3	4
45. Have you needed repeated courses of antibiotics?	1	2	3	4
46. Have you worried about picking up an infection?	1	2	3	4

Attachment 8: 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

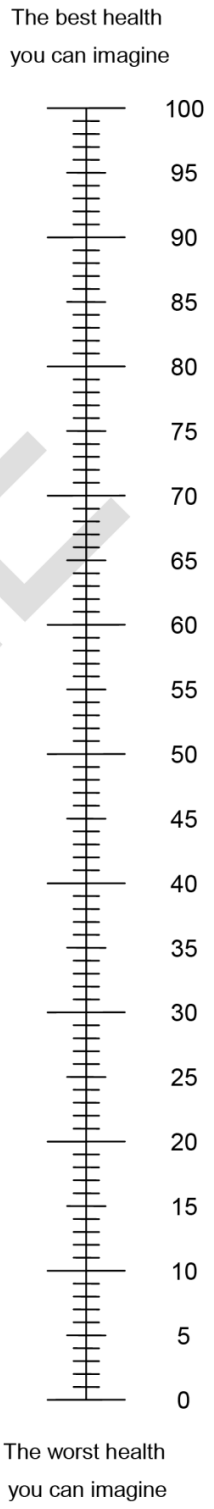
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

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 9: 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
HI7	I feel fatigued	0	1	2	3	4
HI12	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

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Attachment 10: International Workshop on Chronic Lymphocytic Leukemia Criteria for Treatment

Active disease meeting at least 1 of the following IWCLL 2008 criteria for requiring treatment[22]:

a. Evidence of progressive marrow failure as manifested by the development of, or worsening of, anemia or thrombocytopenia;

b. Massive (ie, at least 6 cm below the left costal margin), progressive, or symptomatic splenomegaly;

c. Massive nodes (ie, at least 10 cm in longest diameter), progressive, or symptomatic lymphadenopathy;

d. Progressive lymphocytosis with an increase of more than 50% over a 2-month period or a lymphocyte doubling time (LDT) of less than 6 months (which may be extrapolated). Lymphocyte doubling time can be obtained by linear regression extrapolation of ALCs obtained at intervals of 2 weeks over an observation period of 2 to 3 months. For patients with initial blood lymphocyte counts of less than 30 x 10^9/L (30,000/μL), LDT should not be used as a single parameter to define indication for treatment. In addition, factors contributing to lymphocytosis or lymphadenopathy other than CLL (eg, infections) should be excluded;

e. Autoimmune anemia and/or thrombocytopenia that is poorly responsive to corticosteroids or other standard therapy;

f. Constitutional symptoms, defined as 1 or more of the following disease-related symptoms or signs:

   1) Unintentional weight loss >10% within the previous 6 months prior to 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; or

   4) Night sweats for more than 1 month without evidence of infection.

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): Jessica Vermeulen, MD

Institution: [redacted]ent

Signature: _____ Date: 28 AUG 2017
(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.