

Protocol J2N-OX-JZNP 5.0

A Phase 3 Open-Label, Randomized Study of Pirtobrutinib (LOXO-305) versus Bendamustine plus Rituximab in Untreated Patients with Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (BRUIN CLL-313)

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CLINICAL PROTOCOL LOXO-BTK-20023

A Phase 3 Open-Label, Randomized Study of Pirtobrutinib (LOXO-305) versus Bendamustine plus Rituximab in Untreated Patients with Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (BRUIN-CLL-313)

Investigational Product:	Pirtobrutinib (LOXO-305)
Protocol Number:	LOXO-BTK-20023 (J2N-OX-JZNP)
Development Phase:	3
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EU trial number:	2024-511599-33-00
Sponsor:	Loxo Oncology, Inc., a wholly owned subsidiary of Eli Lilly and Company 281 Tresser Boulevard Stamford, CT 06901

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Approval Date: Protocol Amendment (Version 5.0) Electronically Signed and Approved by Lilly on date provided below.

Document ID: VV-CLIN-115367

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	Date
<i>Previous Version 4.0</i>	<i>25-Aug-2023</i>
<i>Previous Version 3.0</i>	<i>10-Feb-2023</i>
<i>Previous Version 2.0</i>	<i>11-May-2021</i>
<i>Original Protocol (Version 1.0)</i>	<i>16-Mar-2021</i>

Amendment [5.0]

This amendment is considered to be nonsubstantial.

Overall rationale for the amendment

The primary rationale for this amendment is to update the EU trial number.

Section # and Name	Description of Change	Brief Rationale
Title page 1.1. Synopsis	Updated the EU trial number	The trial was inadvertently deleted in the CTIS system and had to be re-registered. This resulted in a new EU trial number assigned to the trial.
6.1. Study Interventions Administered Table 6.1 Intervention Groups and Duration	Updated the last row	Pirtobrutinib has received marketing authorization in EU so this table was updated to reflect authorization status.

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title:

A Phase 3 Open-Label, Randomized Study of Pirtobrutinib (LOXO-305) versus Bendamustine plus Rituximab in Untreated Patients with Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (BRUIN-CLL-313)

Short Title:

A Phase 3 Study Comparing Pirtobrutinib (LOXO-305) to Bendamustine plus Rituximab in Untreated Patients with CLL/SLL

Regulatory Agency Identifier Numbers:

IND#:	139876
EudraCT#:	2021-001234-20
EU trial number:	2024-511599-33-00

Rationale:

The treatment landscape for patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) has evolved over the last 10 years, resulting in markedly improved long-term outcomes (Burger 2020). While chemoimmunotherapy (CIT) had formed the foundation of therapy, more recent insights into the biologic dependence of CLL/SLL on B-cell receptor signaling, as well as anti-apoptotic machinery has led to the successful development of several novel targeted therapies, including agents inhibiting the Bruton's tyrosine kinase (BTK), B-cell lymphoma 2 (BCL2), and phosphoinositide 3-kinase (PI3K) delta. The introduction of these novel agents, in both, treatment naïve and previously treated patients has significantly improved the outcome of patients with CLL (Fischer et al. 2019; Shanafelt et al. 2019; Woyach et al. 2018; Burger et al. 2015). When making treatment decisions, several factors are considered. The covalent BTK inhibitors are given continuously to maximize their therapeutic effect. Additionally, ibrutinib, which is a widely available covalent BTK inhibitor, is less selective against BTK and therefore, exhibits a toxicity profile beyond on-target effect that leads to frequent treatment discontinuation. Further, venetoclax, a BCL2 inhibitor, is approved in certain regions in combination with obinutuzumab in the frontline setting, and with rituximab in patients with relapsed/refractory CLL/SLL. Venetoclax-based therapy can provide patients with the opportunity to receive time-limited therapy. However, venetoclax requires intense monitoring, and in some cases, hospitalization due to the risk of tumor lysis syndrome (TLS) and the need for prophylactic therapy and intravenous (IV) hydration.

While covalent BTK inhibitors and venetoclax-based regimens are increasingly utilized as initial therapy for patients with CLL/SLL, substantial heterogeneity in treatment patterns continue to

exist both globally and in the United States (US). Contemporary prescribing data from a prospective US-based registry of CLL/SLL patients illustrates this point (Mato et al. 2020). In this cohort of 1462 patients enrolled since 2015 (93% from community-based sites), 25% of treatment-naïve CLL/SLL patients who initiated treatment in 2019 received frontline CIT. These data, in addition to other prescribing databases, continue to support the assertion that while the uptake of CIT has declined since the approval of targeted therapies, CIT continues to represent a significant treatment option for this patient population. Of note, bendamustine plus rituximab (BR) was the most frequently used CIT regimen in this registry in the frontline setting.

CIT has served as the foundation for treating patients with CLL/SLL for many years. These regimens were utilized based on several factors including patient age, performance status, comorbid conditions and the disease molecular features. Fludarabine, cyclophosphamide with rituximab (FCR) demonstrated significant activity against CLL/SLL but was associated with significant toxicity including prolonged immune suppression, hence this regimen is reserved to minority of patients with CLL/SLL who are fit, with no significant comorbid conditions, and younger than age 65 years. The CLL10 study was a randomized Phase 3 study that compared bendamustine plus rituximab (BR) to FCR in patients with CLL/SLL who were treatment naïve with no evidence of 17p deletion, and who required therapy per International Workshop on Chronic Lymphocytic Leukemia 2008 (iwCLL 2008; Eichhorst et al. 2016). After a median follow up of 58.2 months, the median PFS of patients treated with BR was 42.3 months. Five-year overall survival (OS) was not different between BR and FCR (80.1% versus 80.9% respectively). Treatment with FCR in patients > 65 years of age was associated with increased incidence of secondary malignancies (32.6% versus 16.8% in FCR versus BR) (Kutsch et al. 2020). This study established BR as the preferred regimen for patients > 65 years of age, or who are < 65 years of age but with comorbid conditions that deems FCR contraindicated. While the follow up is not as mature, the data from the Alliance study A041202 also demonstrated an estimated median PFS of 43 months for patients treated with BR. The Alliance study enrolled patients with CLL/SLL who are treatment naïve, but also included patients with evidence of 17p deletion (8% of patients treated with BR) (Woyach et al. 2018). In both of these studies (CLL10 and Alliance), BR provided the opportunity for time-limited therapy with durable disease control (estimated median PFS of 43 months) and improved treatment free intervals, which supports the ongoing use of BR in the US and globally in the frontline setting (Eichhorst et al. 2016; Woyach et al. 2018).

Pirtobrutinib (LOXO-305):

Pirtobrutinib is an orally available, highly selective, adenosine triphosphate (ATP)-competitive inhibitor of BTK. Pirtobrutinib has single digit nanomolar inhibitory activity against wildtype BTK and the BTK C481S acquired resistance mutation which results from a serine substitution at position 481.

Pirtobrutinib is distinct from the approved BTK inhibitors (ibrutinib, acalabrutinib, and zanubrutinib) on the basis of its selectivity, pharmacologic and pharmacokinetic (PK) properties, and non-covalent binding mode (Brandhuber et al. 2018). These features enable pirtobrutinib to

achieve PK exposures with once daily oral dosing that exceed the BTK-wt 90% inhibitory concentration (IC₉₀) at trough and thus deliver tonic BTK target inhibition throughout the dosing period, regardless of the intrinsic rate of BTK turnover. Moreover, the non-covalent binding mode of pirtobrutinib is unaffected by BTK C481 substitutions, a common mechanism of drug resistance described for all available covalent BTK inhibitors. (Byrd et al. 2013; Woyach et al. 2017; Woyach et al. 2019; Chiron et al. 2014; Xu et al. 2017). Finally, pirtobrutinib is also a highly selective molecule, with more than 300-fold more selectivity for BTK versus 370 other kinases tested and no significant inhibition of non-kinase off-targets at 1 μ M, thus limiting the potential for off-target mediated toxicities.

In a Phase 1/2 study (LOXO-BTK-18001, NCT03740529), pirtobrutinib has demonstrated robust and durable anti-tumor activity against a variety of B-cell malignancies including CLL/SLL, regardless of prior treatment including in patients treated with covalent BTK inhibitors. Of note, this promising activity in CLL/SLL patients has been observed in patients with both wildtype BTK as well as those harboring BTK cysteine residue at position 481 (C481) mutations.

The purpose of this global study is to compare the efficacy and safety of pirtobrutinib administered as a continuous monotherapy versus BR, in patients with previously untreated CLL/SLL with no evidence of 17p deletion, who require therapy per iwCLL 2018 response criteria.

Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate progression-free survival (PFS) of pirtobrutinib as monotherapy (Arm A) compared to BR (Arm B).	Assessed by IRC (Independent Review Committee (IRC)): PFS per International Workshop on Chronic Lymphocytic Leukemia (iwCLL) 2018 response criteria
Secondary	
To evaluate the effectiveness of Arm A compared to Arm B based on overall response rate (ORR) and time to event(s) outcomes	- Assessed by Investigator: - PFS per iwCLL 2018 criteria - Overall survival (OS) - Time to next treatment (TTNT), defined as time from the date of randomization to the date of the next systemic anticancer therapy for CLL/SLL (see Section 9 for full definition). - Assessed by Investigator and IRC: - ORR - Duration of response (DOR)
To evaluate the safety and tolerability of each treatment arm	Including, but not limited to, serious adverse events (SAEs), adverse events (AEs), deaths and clinical laboratory abnormalities per National Cancer Institute Common Terminology Criteria for Adverse Events v5.0 (NCI CTCAE v5.0)
To evaluate the effectiveness of Arm A compared to Arm B based on patient reported outcomes	- Patient reported outcomes of: - Time to worsening (TTW) of CLL/SLL-related symptoms - TTW of physical functioning as measured by the physical function domain of the EORTC-QLQ-C30
Tertiary or Exploratory Objectives	
- To identify biomarkers of response and survival in patients treated in both study arms - To identify mechanisms of resistance to pirtobrutinib - To assess the use of medical resources including hospitalizations and emergency department visits, transfusions, and growth factor support according to the treatment arm - To explore the relationship between pirtobrutinib plasma exposure and selected efficacy and safety outcomes - To compare HRQoL measured by EORTC QLQ-C30 and EQ-5D-5L between the treatment arms	

Overall Design:

LOXO-BTK-20023 (BRUIN-CLL-313) is a Phase 3 global, randomized, open-label study comparing pirtobrutinib as continuous monotherapy (Arm A) to BR (Arm B) in CLL/SLL patients who are treatment naïve. Patients who are treatment naïve and require therapy per iwCLL 2018 criteria with no evidence of 17p deletion will be enrolled if they meet eligibility criteria. The study will enroll approximately 250 patients and will randomize patients in a 1:1 ratio. Patients will be stratified based on immunoglobulin heavy chain variable region gene

(IGHV) mutation status (mutated versus unmutated), and on Rai stage (low/intermediate versus high).

This study will enroll adult CLL/SLL patients with an indication for treatment as defined by the iwCLL 2018 criteria (Hallek et al. 2018; Cheson et al. 2012; Section 10.7, Appendix 7). Patients assigned to oral pirtobrutinib will receive pirtobrutinib continuously until discontinuation criteria are met (Section 7.1). Patients assigned to BR will receive up to 6 cycles of both agents IV unless they experience unacceptable toxicity or progression, at which time patients will discontinue treatment. Patients who complete the full course of BR or discontinue prior to completing 6 cycles due to intolerance, will be followed until progression, death, lost to follow-up, withdrawal of consent, or study completion. Patients will be allowed to cross over from Arm B to Arm A upon confirmation of progressive disease (PD) by Independent Review Committee (IRC), and if they meet the eligibility criteria for crossover (Section 5.3). Patients who have PD per the Investigators' assessment but not IRC, are not eligible for crossover until they meet IRC PD criteria. Patients who progress on Arm A, may be allowed to continue treatment beyond progression if the patient is tolerating study treatment and, in the opinion of the Investigator, is deriving ongoing clinical benefit. Patients considered for treatment beyond progression must not have symptomatic progression (examples include patients with progression based on lymphocytosis in the absence of evidence of bone marrow failure, or patients with isolated asymptomatic nodal progression). Continuation of treatment on Arm A post-progression must be approved by the Sponsor. Patients will need to be consented for treatment beyond progression on pirtobrutinib. Patients who discontinue treatment on either arm for any reason other than PD, death, lost to follow-up, or withdrawal of consent will be followed for tumor assessment until PD, regardless of whether the patient receives a new anticancer therapy. Upon PD, all patients will then be placed on Long-Term Follow-up (LTFU) every 16 weeks for the first 2 years, and every 24 weeks thereafter until death, lost to follow-up, withdrawal of consent, or study completion.

Pirtobrutinib: Patients randomized to Arm A will receive treatment with pirtobrutinib monotherapy.

Bendamustine plus rituximab (BR): Patients randomized to Arm B will receive treatment as outlined below in Study Treatment Groups and detailed in Section 6.1.3.

On days when bendamustine and rituximab are to be administered, rituximab will be administered prior to bendamustine.

Disclosure Statement:

This is a randomized, active treatment study with 2 arms where the patient and Investigator will not be blinded.

Study Population:

In general, an individual may take part in this study if they meet the following criteria:

Age

- Are 18 years or older per local regulations at time of enrollment.

Type of Patient and Disease Characteristics

- Have a confirmed diagnosis by redacted local laboratory report of CLL/SLL as defined by iwCLL 2018 criteria, including the following:
 - a) B cells must:
 - (1) co-express CD5 and CD23
 - (2) express at least one B cell antigen (CD19 or CD20), and
 - (3) be either κ or λ light-chain restricted.Atypical cases may be considered with Sponsor approval.
 - b) $\geq 5 \times 10^9$ B lymphocytes/L (5000/ μ L) in the peripheral blood for CLL patients. For SLL patients, $< 5 \times 10^9$ B lymphocytes/L (5000/ μ L) in the peripheral blood is allowed.
 - c) Prolymphocytes may comprise $\leq 55\%$ of blood lymphocytes (for CLL patients).

Number of Patients:

Approximately 250 patients will be randomized 1:1, Arm A: Arm B.

Study Treatment Groups:

	Arm A pirtobrutinib	Arm B bendamustine plus rituximab (BR)	
Treatment	pirtobrutinib	bendamustine	rituximab
Dose	200 mg	90 mg/m ²	375 mg/m ² on Cycle 1 Day 1 (C1D1) and then 500 mg/m ²
Schedule	QD in 28 -day continuous cycles	90 mg/m ² on Day 1 and Day 2 of each 28-day cycle, Cycles 1 to 6	375 mg/m ² on C1D1 and then 500 mg/m ² given on Day 1 of each 28-day cycle, Cycles 2 to 6
Route	Oral	Intravenous (IV)	(IV)

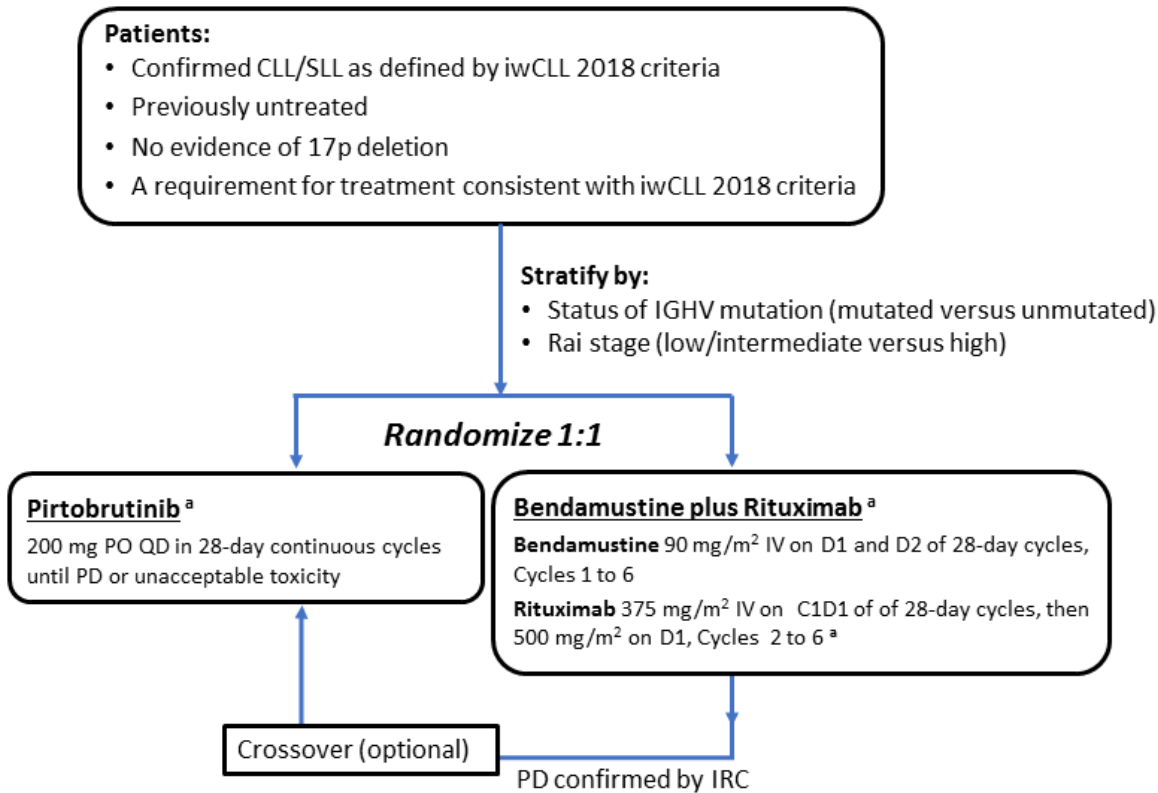
Ethical considerations of benefit/risk:

During the Phase 1/2 study, pirtobrutinib has demonstrated a favorable safety profile and positive efficacy. Additionally, considering the measures taken to ensure the participants in this study are safe, the potential risks from taking part in the study are justified by the potential benefits for individuals with chronic lymphocytic leukemia/small lymphocytic lymphoma.

Data Monitoring Committee:

A Data Monitoring Committee (DMC) will be utilized to review aggregate safety data for this study. Refer to the DMC charter for further information.

1.2. Study Design Schema



a Detailed study treatment dosing instructions are provided in Section 6.1.

1.3. Schedule of Assessments

This section includes Schedules of Assessments (SoAs) for patients receiving the following treatments:

- Arm A: pirtobrutinib (Section [1.3.1](#))
- Arm B: bendamustine plus rituximab (BR) (Section [1.3.2](#))
- Optional crossover treatment (for patients crossing over from Arm B to Arm A) (Section [1.3.3](#))

Additional SoAs include the following:

- The Patient Reported Outcomes (PRO) SoA is provided in Section [1.3.4](#).

1.3.1. Schedule of Assessments for Arm A: Pirtobrutinib Monotherapy

Schedule of Assessments for Arm A: Pirtobrutinib Monotherapy								
Study Period	Baseline	Study Treatment (Cycle = 28 days)			Post-Study Treatment Discontinuation			Instructions
Evaluation	Screening	Cycle 1	Cycles 2-6	Cycle 7 +	EOT	SFU	LTFU	For Cycle 7, only dispensation of pirtobrutinib will be done at the clinic visit. For Cycle 8, there will be no scheduled clinic visit.
Visit Window	Up to 28 days	Day 1	Day 1 (± 7 days)	Day 1 (± 7 days) Q16W from C1D1 for 2 years and Q24W thereafter	0-7 Days of last dose or decision to terminate treatment	28 Days (+ 7 days) after last dose or decision to terminate treatment	Q16W for first 2 years (relative to C1D1) and Q24W thereafter (± 4 weeks)	An EOT assessment should occur within 7 days of last dose of study treatment or decision to terminate study treatment.
Informed consent	X							The ICF must be signed before any protocol-specified procedures are performed. Refer to Section 10.1.2 Appendix 1
Medical history	X							- All ongoing conditions and relevant past surgical and medical history should be collected. Refer to Section 8.2 - Malignancy history should be collected regarding disease under study, and any history of other malignancy
Documentation of diagnosis and relevant biomarkers	X							- De-identified pathology report(s) may be requested to confirm eligibility - Reports regarding status of any known CLL relevant biomarkers should be provided if available (e.g., IGHV, TP53 mutation, complex karyotype, del 11q)

Schedule of Assessments for Arm A: Pirtobrutinib Monotherapy								
Study Period	Baseline	Study Treatment (Cycle = 28 days)			Post-Study Treatment Discontinuation			Instructions
Evaluation	Screening	Cycle 1	Cycles 2-6	Cycle 7 +	EOT	SFU	LTFU	For Cycle 7, only dispensation of pirtobrutinib will be done at the clinic visit. For Cycle 8, there will be no scheduled clinic visit.
Visit Window	Up to 28 days	Day 1	Day 1 (± 7 days)	Day 1 (± 7 days) Q16W from C1D1 for 2 years and Q24W thereafter	0-7 Days of last dose or decision to terminate treatment	28 Days (+ 7 days) after last dose or decision to terminate treatment	Q16W for first 2 years (relative to C1D1) and Q24W thereafter (± 4 weeks)	An EOT assessment should occur within 7 days of last dose of study treatment or decision to terminate study treatment.
Physical examination	X	X	X	X	X	X	X	- Complete PE includes height (only at Screening), weight, basic neurological examination and review of relevant symptoms at Screening (refer to Section 8.4.2) - Symptom-targeted PE should be limited to systems of primary relevance such as, cardiovascular, respiratory, and those associated with tumor assessment (lymph nodes, liver, and spleen) and may be performed at other timepoints; include weight as clinically indicated throughout the trial - Screening results obtained within 3 days of C1D1 are acceptable as C1D1 results - Response assessments include PE (disease and symptom-focused), hematology, and CT or MRI, as described in iwCLL 2018 - PE, hematology, and CT or MRI should occur at indicated intervals relative to C1D1, regardless of any treatment delays or interruptions - For patients who discontinue treatment prior to documented PD, LTFU continues until documented PD, even if started on alternative cancer therapy
ECOG PS	X	X	X	X	X	X		

Schedule of Assessments for Arm A: Pirtobrutinib Monotherapy								
Study Period	Baseline	Study Treatment (Cycle = 28 days)			Post-Study Treatment Discontinuation			Instructions
Evaluation	Screening	Cycle 1	Cycles 2-6	Cycle 7 +	EOT	SFU	LTFU	For Cycle 7, only dispensation of pirtobrutinib will be done at the clinic visit. For Cycle 8, there will be no scheduled clinic visit.
Visit Window	Up to 28 days	Day 1	Day 1 (± 7 days)	Day 1 (± 7 days) Q16W from C1D1 for 2 years and Q24W thereafter	0-7 Days of last dose or decision to terminate treatment	28 Days (+ 7 days) after last dose or decision to terminate treatment	Q16W for first 2 years (relative to C1D1) and Q24W thereafter (± 4 weeks)	An EOT assessment should occur within 7 days of last dose of study treatment or decision to terminate study treatment.
Vital signs	X	X	X	X	X	X		Includes systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature
Results of tests in the section below are <u>required for eligibility determination and enrollment</u>								
17p deletion evaluation	X	X						- Local 17p deletion results by FISH can be used to determine the eligibility if tested within 6 months of the date ICF was signed - If local 17p deletion results by FISH are not available at Screening, a sample should be collected and tested locally or centrally prior to enrollment - The C1D1 sample is collected for exploratory purposes
IGHV	X	X						- IGHV results will be used for stratification. When results are not available, a sample should be collected and tested locally or centrally for stratification - The C1D1 sample is collected for exploratory purposes

Schedule of Assessments for Arm A: Pirtobrutinib Monotherapy								
Study Period	Baseline	Study Treatment (Cycle = 28 days)			Post-Study Treatment Discontinuation			Instructions
Evaluation	Screening	Cycle 1	Cycles 2-6	Cycle 7 +	EOT	SFU	LTFU	For Cycle 7, only dispensation of pirtobrutinib will be done at the clinic visit. For Cycle 8, there will be no scheduled clinic visit.
Visit Window	Up to 28 days	Day 1	Day 1 (± 7 days)	Day 1 (± 7 days) Q16W from C1D1 for 2 years and Q24W thereafter	0-7 Days of last dose or decision to terminate treatment	28 Days (+ 7 days) after last dose or decision to terminate treatment	Q16W for first 2 years (relative to C1D1) and Q24W thereafter (± 4 weeks)	An EOT assessment should occur within 7 days of last dose of study treatment or decision to terminate study treatment.
CMV	X							CMV IgG, IgM and DNA PCR (Section 8.4.5.5)
12-lead ECG	X	X	X	X				Obtain ECGs at specified visits and when patients are symptomatic. Refer to Section 8.4.4. ECGs should be collected: - At Screening, triplicate ECG - C1D1: pre-dose and at 2 hours post dose (single ECG) - If an unscheduled ECG is done at any time, an electrolyte panel (i.e., calcium, magnesium, and potassium) must be done to coincide with the ECG - If a clinically significant arrhythmia is detected, details must be entered in the dedicated EDC pages, and the Arrhythmia Collection Form must be sent to the study mailbox

Schedule of Assessments for Arm A: Pirtobrutinib Monotherapy								
Study Period	Baseline	Study Treatment (Cycle = 28 days)			Post-Study Treatment Discontinuation			Instructions
Evaluation	Screening	Cycle 1	Cycles 2-6	Cycle 7 +	EOT	SFU	LTFU	For Cycle 7, only dispensation of pirtobrutinib will be done at the clinic visit. For Cycle 8, there will be no scheduled clinic visit.
Visit Window	Up to 28 days	Day 1	Day 1 (± 7 days)	Day 1 (± 7 days) Q16W from C1D1 for 2 years and Q24W thereafter	0-7 Days of last dose or decision to terminate treatment	28 Days (+ 7 days) after last dose or decision to terminate treatment	Q16W for first 2 years (relative to C1D1) and Q24W thereafter (± 4 weeks)	An EOT assessment should occur within 7 days of last dose of study treatment or decision to terminate study treatment.
Central hematology		X	C5D1	X	X		X	- Includes hemoglobin, hematocrit, RBC, WBC and platelet count, percent or absolute differential (neutrophils, lymphocytes, basophils, eosinophils, and monocytes). - Screening results obtained within 3 days of C1D1 are acceptable as C1D1 results - On days when hematology is required for both safety and response assessments, samples must also be submitted to the central laboratory, including C1D1
Local hematology	X	X	X	X	X	X	X	- Response assessments include PE (disease and symptom-focused), hematology, and CT or MRI, as described in iwCLL 2018 - PE, hematology, and CT or MRI should occur at indicated intervals relative to C1D1, regardless of any treatment delays or interruptions - For patients who discontinue treatment prior to documented PD, LTFU continues until documented PD, even if started on alternative cancer therapy - Refer to Section 10.2 Appendix 2 Clinical Laboratory Tests

Schedule of Assessments for Arm A: Pirtobrutinib Monotherapy								
Study Period	Baseline	Study Treatment (Cycle = 28 days)			Post-Study Treatment Discontinuation			Instructions
Evaluation	Screening	Cycle 1	Cycles 2-6	Cycle 7 +	EOT	SFU	LTFU	For Cycle 7, only dispensation of pirtobrutinib will be done at the clinic visit. For Cycle 8, there will be no scheduled clinic visit.
Visit Window	Up to 28 days	Day 1	Day 1 (± 7 days)	Day 1 (± 7 days) Q16W from C1D1 for 2 years and Q24W thereafter	0-7 Days of last dose or decision to terminate treatment	28 Days (+ 7 days) after last dose or decision to terminate treatment	Q16W for first 2 years (relative to C1D1) and Q24W thereafter (± 4 weeks)	An EOT assessment should occur within 7 days of last dose of study treatment or decision to terminate study treatment.
Blood chemistries	X	X	X	X	X	X		- Blood chemistry from serum or plasma should include assessment of: sodium, potassium, chloride, glucose, creatinine, total protein, albumin, total bilirubin, ALT and AST - In addition, LDH, calcium, magnesium, phosphorus and uric acid are required at Screening and Day 1 of C1 to C6 - Refer to Section 8.4.5.10 for hepatic safety monitoring - Screening results within 3 days of C1D1 are acceptable as C1D1 results - Direct (or indirect) bilirubin should be performed any time total bilirubin is abnormal - Refer to Section 10.2 Appendix 2 Clinical Laboratory Tests
Coagulation panel	X	As clinically indicated						- aPTT and PT (or INR) - Refer to Section 10.2 Appendix 2 Clinical Laboratory Tests
Hepatitis B/C active disease status	X							- HBV and HCV testing will be used to determine if patients have active infection - Refer to Section 5.2 for exclusions

Schedule of Assessments for Arm A: Pirtobrutinib Monotherapy								
Study Period	Baseline	Study Treatment (Cycle = 28 days)			Post-Study Treatment Discontinuation			Instructions
Evaluation	Screening	Cycle 1	Cycles 2-6	Cycle 7 +	EOT	SFU	LTFU	For Cycle 7, only dispensation of pirtobrutinib will be done at the clinic visit. For Cycle 8, there will be no scheduled clinic visit.
Visit Window	Up to 28 days	Day 1	Day 1 (± 7 days)	Day 1 (± 7 days) Q16W from C1D1 for 2 years and Q24W thereafter	0-7 Days of last dose or decision to terminate treatment	28 Days (+ 7 days) after last dose or decision to terminate treatment	Q16W for first 2 years (relative to C1D1) and Q24W thereafter (± 4 weeks)	An EOT assessment should occur within 7 days of last dose of study treatment or decision to terminate study treatment.
Serum or urine pregnancy test (WOCBP only)	X	X	X	X	X	X		- Perform within 24 hours of first dose of study treatment, and as indicated in table, or as required per local regulations and/or institutional guidelines; refer to Section 10.3 Appendix 3 - Refer to Section 10.2 Appendix 2 Clinical Laboratory Tests
Urinalysis	X	As clinically indicated						- Dipstick analysis is acceptable and should include color, specific gravity, pH, glucose, bilirubin, occult blood, protein, leukocytes, and urobilinogen - Refer to Section 10.2 Appendix 2 Clinical Laboratory Tests
Documentation or sampling of the following are required during Screening, but results <u>not required prior to enrollment</u>								
β2 microglobulin	X							
Serum immunoglobulins	X							- IgG, IgA, IgM - Refer to Section 10.2 Appendix 2 Clinical Laboratory Tests

Schedule of Assessments for Arm A: Pirtobrutinib Monotherapy								
Study Period	Baseline	Study Treatment (Cycle = 28 days)			Post-Study Treatment Discontinuation			Instructions
Evaluation	Screening	Cycle 1	Cycles 2-6	Cycle 7 +	EOT	SFU	LTFU	For Cycle 7, only dispensation of pirtobrutinib will be done at the clinic visit. For Cycle 8, there will be no scheduled clinic visit.
Visit Window	Up to 28 days	Day 1	Day 1 (± 7 days)	Day 1 (± 7 days) Q16W from C1D1 for 2 years and Q24W thereafter	0-7 Days of last dose or decision to terminate treatment	28 Days (+ 7 days) after last dose or decision to terminate treatment	Q16W for first 2 years (relative to C1D1) and Q24W thereafter (± 4 weeks)	An EOT assessment should occur within 7 days of last dose of study treatment or decision to terminate study treatment.
Bone marrow aspirate and biopsy	X		Within 4-8 weeks of confirmed CR by scan and peripheral blood assessment		To confirm PD (optional)			- Refer to Section 8.10.1 - In extenuating circumstances, the requirement for collection of a bone marrow biopsy and aspirate at Screening may be waived based on approval from the Sponsor if the procedure has occurred within 90 days of the planned date of randomization - Whenever feasible, investigator response assessment should rely on local bone marrow results

Schedule of Assessments for Arm A: Pirtobrutinib Monotherapy								
Study Period	Baseline	Study Treatment (Cycle = 28 days)			Post-Study Treatment Discontinuation			Instructions
Evaluation	Screening	Cycle 1	Cycles 2-6	Cycle 7 +	EOT	SFU	LTFU	For Cycle 7, only dispensation of pirtobrutinib will be done at the clinic visit. For Cycle 8, there will be no scheduled clinic visit.
Visit Window	Up to 28 days	Day 1	Day 1 (± 7 days)	Day 1 (± 7 days) Q16W from C1D1 for 2 years and Q24W thereafter	0-7 Days of last dose or decision to terminate treatment	28 Days (+ 7 days) after last dose or decision to terminate treatment	Q16W for first 2 years (relative to C1D1) and Q24W thereafter (± 4 weeks)	An EOT assessment should occur within 7 days of last dose of study treatment or decision to terminate study treatment.
CT or MRI	X		C5D1	X	X		X	- Refer to Section 8.3.1 for details. - CT scans will be performed every 16 weeks for 2 years and every 24 weeks beyond 2 years; CT scans in between these visits may be performed if PD is suspected - Response assessments include PE (disease and symptom-focused), hematology, and CT or MRI, as described in iwCLL 2018 - PE, hematology, and CT or MRI should occur at indicated intervals relative to C1D1, regardless of any treatment delays or interruptions - For patients who discontinue treatment prior to documented PD, LTFU continues until documented PD, even if started on alternative cancer therapy - A central radiology vendor will be used to collect and store images for IRC review
Saliva for germline DNA (optional)	X							Collect only if patient has consented to collection and testing; refer to Laboratory Manual for details
Blood samples for PK			X					Pre-dose sample only; refer to Laboratory Manual for details

Schedule of Assessments for Arm A: Pirtobrutinib Monotherapy								
Study Period	Baseline	Study Treatment (Cycle = 28 days)			Post-Study Treatment Discontinuation			Instructions
Evaluation	Screening	Cycle 1	Cycles 2-6	Cycle 7 +	EOT	SFU	LTFU	For Cycle 7, only dispensation of pirtobrutinib will be done at the clinic visit. For Cycle 8, there will be no scheduled clinic visit.
Visit Window	Up to 28 days	Day 1	Day 1 (± 7 days)	Day 1 (± 7 days) Q16W from C1D1 for 2 years and Q24W thereafter	0-7 Days of last dose or decision to terminate treatment	28 Days (+ 7 days) after last dose or decision to terminate treatment	Q16W for first 2 years (relative to C1D1) and Q24W thereafter (± 4 weeks)	An EOT assessment should occur within 7 days of last dose of study treatment or decision to terminate study treatment.
Whole blood for correlative studies		X	C2D1 and C4D1	X	X		X (Upon confirmation of PD)	• Samples to be provided for exploratory biomarker analyses (Section 8.10.5); refer to Laboratory Manual for details • If a patient discontinues treatment for reasons other than PD, a sample of whole blood should be collected during follow up when PD is confirmed • At the time of bone marrow biopsy to confirm CR, an additional collection of whole blood is required for exploratory biomarker analyses
Pirtobrutinib administration								• 200 mg PO administered QD (continuous); refer to Table 6.1 • C1D1 should occur within 7 business days after randomization • Date of last dose and date of decision for end of treatment must be recorded in EDC • Pirtobrutinib will be dispensed at clinic visits for Cycles 1-6, and then Q8W for Cycles 7-24, and then Q12W starting C25
Patient dosing diary								
Concomitant medication								Refer to Section 6.5

Schedule of Assessments for Arm A: Pirtobrutinib Monotherapy								
Study Period	Baseline	Study Treatment (Cycle = 28 days)			Post-Study Treatment Discontinuation			Instructions
Evaluation	Screening	Cycle 1	Cycles 2-6	Cycle 7 +	EOT	SFU	LTFU	For Cycle 7, only dispensation of pirtobrutinib will be done at the clinic visit. For Cycle 8, there will be no scheduled clinic visit.
Visit Window	Up to 28 days	Day 1	Day 1 (± 7 days)	Day 1 (± 7 days) Q16W from C1D1 for 2 years and Q24W thereafter	0-7 Days of last dose or decision to terminate treatment	28 Days (+ 7 days) after last dose or decision to terminate treatment	Q16W for first 2 years (relative to C1D1) and Q24W thereafter (± 4 weeks)	An EOT assessment should occur within 7 days of last dose of study treatment or decision to terminate study treatment.
Adverse events								- Collect SAEs from the time of ICF signing through SFU. SAEs that occur prior to the first dose are considered medical history unless the SAE develops or worsens due to study-related procedures - All SAEs that the Investigator considers related to the study drug occurring after SFU must be reported to the Sponsor - All SAEs must be reported to Clinical Safety within 24 hours of knowledge of the event. - Second primary malignancy (SPM) events will continue to be reported up to 5 years since the start of the study drug regardless of the seriousness or causal attribution to treatment (Section 8.6.6) - Collect AEs from the time of dosing through SFU
Medical resources utilization								- Hospitalizations, emergency department visits, blood product transfusions, and hematopoietic growth factor use will be collected - Patients (on both treatment arms) need to be assessed Q16W for a total of 2 years, and then Q24W thereafter until PD or 48 months post C1D1 whichever occurs first

Schedule of Assessments for Arm A: Pirtobrutinib Monotherapy								
Study Period	Baseline	Study Treatment (Cycle = 28 days)			Post-Study Treatment Discontinuation			Instructions
Evaluation	Screening	Cycle 1	Cycles 2-6	Cycle 7 +	EOT	SFU	LTFU	For Cycle 7, only dispensation of pirtobrutinib will be done at the clinic visit. For Cycle 8, there will be no scheduled clinic visit.
Visit Window	Up to 28 days	Day 1	Day 1 (± 7 days)	Day 1 (± 7 days) Q16W from C1D1 for 2 years and Q24W thereafter	0-7 Days of last dose or decision to terminate treatment	28 Days (+ 7 days) after last dose or decision to terminate treatment	Q16W for first 2 years (relative to C1D1) and Q24W thereafter (± 4 weeks)	An EOT assessment should occur within 7 days of last dose of study treatment or decision to terminate study treatment.
Patient reported outcomes								- Refer to Section 1.3.4 for details - Patients (on both treatment arms) need to be assessed according to Section 1.3.4 until PD or 48 months post C1D1 whichever occurs first
Survival status							X	- Survival information may be collected via telephone if no procedures are required. - Subsequent anticancer therapy information should be collected every 16 weeks for the first 2 years relative to C1D1 and approximately every 24 weeks thereafter until death or study completion

1.3.2. Schedule of Assessments for Arm B: Bendamustine plus Rituximab (BR)

Schedule of Assessments for Arm B: Bendamustine plus Rituximab (BR)									
Study Period	Baseline	Study Treatment (Cycle = 28 days)				Post-Study Treatment Discontinuation			Instructions
Evaluation	Screening	Cycle 1		Cycles 2-6		EOT	SFU	LTFU	Patients will proceed to EOT after the Cycle 6 treatment
Visit Window	Up to 28 days	Day 1	Day 2	Day 1 (± 7 days)	Day 2	+ 7 Days of last dose or decision to terminate treatment	28 Days (+ 7 days) after last dose or decision to terminate treatment	Q16W for first 2 years (relative to C1D1) and Q24W thereafter (± 4 weeks)	An EOT assessment should occur within 7 days of last dose of study treatment or decisions to terminate study treatment.
Informed consent	X								The ICF must be signed before any protocol-specified procedures are performed. Refer to Section 10.1.2 Appendix 1
Medical history	X								- All ongoing conditions and relevant past surgical and medical history should be collected. Refer to Section 8.2 - Malignancy history should be collected regarding disease under study, and any history of other malignancy
Documentation of diagnosis and relevant biomarkers	X								- De-identified pathology report(s) may be requested to confirm eligibility - Reports regarding status of any known CLL relevant biomarkers should be provided if available (e.g., IGHV, TP53 mutation, complex karyotype, del 11q)
Physical examination	X	X		X		X	X	X	Complete PE includes height (only at Screening), weight, basic neurological examination and review of relevant symptoms at Screening (refer to Section 8.4.2)

Schedule of Assessments for Arm B: Bendamustine plus Rituximab (BR)									
Study Period	Baseline	Study Treatment (Cycle = 28 days)				Post-Study Treatment Discontinuation			Instructions
Evaluation	Screening	Cycle 1		Cycles 2-6		EOT	SFU	LTFU	Patients will proceed to EOT after the Cycle 6 treatment
Visit Window	Up to 28 days	Day 1	Day 2	Day 1 (± 7 days)	Day 2	+ 7 Days of last dose or decision to terminate treatment	28 Days (+ 7 days) after last dose or decision to terminate treatment	Q16W for first 2 years (relative to C1D1) and Q24W thereafter (± 4 weeks)	An EOT assessment should occur within 7 days of last dose of study treatment or decisions to terminate study treatment.
									• Symptom-targeted PE should be limited to systems of primary relevance such as, cardiovascular, respiratory, and those associated with tumor assessment (lymph nodes, liver, and spleen) and may be performed at other timepoints; include weight as clinically indicated throughout the trial • Screening results obtained within 3 days of C1D1 are acceptable as C1D1 results • Response assessments include PE (disease and symptom-focused), hematology, and CT or MRI, as described in iwCLL 2018 • PE, hematology, and CT or MRI should occur at indicated intervals relative to C1D1, regardless of any treatment delays or interruptions • For patients who discontinue treatment prior to documented PD, LTFU continues until documented PD, even if started on alternative cancer therapy
ECOG PS	X	X		X		X	X		
Vital signs	X	X	X	X	X	X	X		• Includes systolic and diastolic blood pressure, heart rate, respiratory rate and body temperature

Schedule of Assessments for Arm B: Bendamustine plus Rituximab (BR)									
Study Period	Baseline	Study Treatment (Cycle = 28 days)				Post-Study Treatment Discontinuation			Instructions
Evaluation	Screening	Cycle 1		Cycles 2-6		EOT	SFU	LTFU	Patients will proceed to EOT after the Cycle 6 treatment
Visit Window	Up to 28 days	Day 1	Day 2	Day 1 (± 7 days)	Day 2	+ 7 Days of last dose or decision to terminate treatment	28 Days (+ 7 days) after last dose or decision to terminate treatment	Q16W for first 2 years (relative to C1D1) and Q24W thereafter (± 4 weeks)	An EOT assessment should occur within 7 days of last dose of study treatment or decisions to terminate study treatment.
Results of tests in the section below are required for eligibility determination and enrollment									
17p deletion evaluation	X	X							- Local 17p deletion results by FISH can be used to determine the eligibility if tested within 6 months of the date ICF was signed - If local 17p deletion results by FISH are not available at Screening, a sample should be collected and tested locally or centrally prior to enrollment - The C1D1 sample is collected for exploratory purposes
IGHV	X	X							- IGHV results will be used for stratification. When results are not available, a sample should be collected and tested locally or centrally for stratification - The C1D1 sample is collected for exploratory purposes
CMV	X								CMV IgG, IgM and DNA PCR (Section 8.4.5.5)

Schedule of Assessments for Arm B: Bendamustine plus Rituximab (BR)									
Study Period	Baseline	Study Treatment (Cycle = 28 days)				Post-Study Treatment Discontinuation			Instructions
Evaluation	Screening	Cycle 1		Cycles 2-6		EOT	SFU	LTFU	Patients will proceed to EOT after the Cycle 6 treatment
Visit Window	Up to 28 days	Day 1	Day 2	Day 1 (± 7 days)	Day 2	+ 7 Days of last dose or decision to terminate treatment	28 Days (+ 7 days) after last dose or decision to terminate treatment	Q16W for first 2 years (relative to C1D1) and Q24W thereafter (± 4 weeks)	An EOT assessment should occur within 7 days of last dose of study treatment or decisions to terminate study treatment.
12-lead ECG	X								- Obtain ECGs at specified visit. Refer to Section 8.4.4 - At Screening, triplicate ECG should be collected - If a clinically significant arrhythmia is detected, details must be entered in the dedicated EDC pages, and the Arrhythmia Collection Form must be sent to the study mailbox
Local hematology	X	X		X		X	X	X	- Includes hemoglobin, hematocrit, RBC, WBC and platelet count, percent or absolute differential (neutrophils, lymphocytes, basophils, eosinophils, and monocytes) - Screening results obtained within 3 days of C1D1 are acceptable as C1D1 results - On days when hematology is required for both safety and response assessments, samples must also be submitted to the central laboratory, including C1D1

Schedule of Assessments for Arm B: Bendamustine plus Rituximab (BR)									
Study Period	Baseline	Study Treatment (Cycle = 28 days)				Post-Study Treatment Discontinuation			Instructions
Evaluation	Screening	Cycle 1		Cycles 2-6		EOT	SFU	LTFU	Patients will proceed to EOT after the Cycle 6 treatment
Visit Window	Up to 28 days	Day 1	Day 2	Day 1 (± 7 days)	Day 2	+ 7 Days of last dose or decision to terminate treatment	28 Days (+ 7 days) after last dose or decision to terminate treatment	Q16W for first 2 years (relative to C1D1) and Q24W thereafter (± 4 weeks)	An EOT assessment should occur within 7 days of last dose of study treatment or decisions to terminate study treatment.
Central hematology		X		C5D1		X		X	• Response assessments include PE (disease and symptom-focused), hematology, and CT or MRI, as described in iwCLL 2018 • PE, hematology, and CT or MRI should occur at indicated intervals relative to C1D1, regardless of any treatment delays or interruptions • For patients who discontinue treatment prior to documented PD, LTFU continues until documented PD, even if started on alternative cancer therapy • Refer to Section 10.2 Appendix 2 Clinical Laboratory Tests
Blood chemistries	X	X		X		X	X		• Blood chemistry from serum or plasma should include assessment of: sodium, potassium, chloride, glucose, creatinine, total protein, albumin, total bilirubin, ALT and AST • In addition, LDH, calcium, magnesium, phosphorus and uric acid are required at Screening and Day 1 of C1 to C6 • Screening results within 3 days of C1D1 are acceptable as C1D1 results • Refer to Section 10.2 Appendix 2 Clinical Laboratory Tests

Schedule of Assessments for Arm B: Bendamustine plus Rituximab (BR)									
Study Period	Baseline	Study Treatment (Cycle = 28 days)				Post-Study Treatment Discontinuation			Instructions
Evaluation	Screening	Cycle 1		Cycles 2-6		EOT	SFU	LTFU	Patients will proceed to EOT after the Cycle 6 treatment
Visit Window	Up to 28 days	Day 1	Day 2	Day 1 (± 7 days)	Day 2	+ 7 Days of last dose or decision to terminate treatment	28 Days (+ 7 days) after last dose or decision to terminate treatment	Q16W for first 2 years (relative to C1D1) and Q24W thereafter (± 4 weeks)	An EOT assessment should occur within 7 days of last dose of study treatment or decisions to terminate study treatment.
Coagulation panel	X	As clinically indicated							- aPTT and PT (or INR) - Refer to Section 10.2 Appendix 2 Clinical Laboratory Tests
Hepatitis B/C active disease status	X								- HBV and HCV testing to determine if patients have active infection - Refer to Section 5.2 for exclusions
Serum or urine pregnancy test (WOCBP only)	X	X		X		X	X	X	- Perform within 24 hours of first dose of study treatment, and as indicated in table, or as required per local regulations and/or institutional guidelines; refer to Section 10.3 Appendix 3 - Refer to Section 10.2 Appendix 2 Clinical Laboratory Tests
Urinalysis	X	As clinically indicated							- Dipstick analysis is acceptable and should include color, specific gravity, pH, glucose, bilirubin, occult blood, protein, leukocytes, and urobilinogen - Refer to Section 10.2 Appendix 2 Clinical Laboratory Tests

Schedule of Assessments for Arm B: Bendamustine plus Rituximab (BR)									
Study Period	Baseline	Study Treatment (Cycle = 28 days)				Post-Study Treatment Discontinuation			Instructions
Evaluation	Screening	Cycle 1		Cycles 2-6		EOT	SFU	LTFU	Patients will proceed to EOT after the Cycle 6 treatment
Visit Window	Up to 28 days	Day 1	Day 2	Day 1 (± 7 days)	Day 2	+ 7 Days of last dose or decision to terminate treatment	28 Days (+ 7 days) after last dose or decision to terminate treatment	Q16W for first 2 years (relative to C1D1) and Q24W thereafter (± 4 weeks)	An EOT assessment should occur within 7 days of last dose of study treatment or decisions to terminate study treatment.
Documentation or sampling of the following are required during Screening, but results not required prior to enrollment									
β2 microglobulin	X								
Serum immunoglobulins	X								• IgG, IgA, IgM • Refer to Section 10.2 Appendix 2 Clinical Laboratory Tests
Bone marrow aspirate and biopsy	X			Within 4-8 weeks of confirmed CR by scan and peripheral blood assessment		To confirm PD (optional)			• Refer to Section 8.10.1 • In extenuating circumstances, the requirement for collection of a bone marrow biopsy and aspirate at Screening may be waived based on approval from the Sponsor if the procedure has occurred within 90 days of the planned date of randomization • Whenever feasible, response assessment of CR should rely on local bone marrow results
CT or MRI	X			C5D1				X	• Refer to Section 8.3.1 for details. • CT scans will be performed every 16 weeks for 2 years and every 24 weeks beyond 2 years; CT scans in between these visits may be performed if PD is suspected • Response assessments include PE (disease and symptom-focused), hematology, and CT or MRI, as described in iwCLL 2018 • PE, hematology, and CT or MRI should occur at indicated intervals relative to

Schedule of Assessments for Arm B: Bendamustine plus Rituximab (BR)									
Study Period	Baseline	Study Treatment (Cycle = 28 days)				Post-Study Treatment Discontinuation			Instructions
Evaluation	Screening	Cycle 1		Cycles 2-6		EOT	SFU	LTFU	Patients will proceed to EOT after the Cycle 6 treatment
Visit Window	Up to 28 days	Day 1	Day 2	Day 1 (± 7 days)	Day 2	+ 7 Days of last dose or decision to terminate treatment	28 Days (+ 7 days) after last dose or decision to terminate treatment	Q16W for first 2 years (relative to C1D1) and Q24W thereafter (± 4 weeks)	An EOT assessment should occur within 7 days of last dose of study treatment or decisions to terminate study treatment.
									C1D1, regardless of any treatment delays or interruptions - For patients who discontinue treatment prior to documented PD, LTFU continues until documented PD, even if started on alternative cancer therapy - A central radiology vendor will be used to collect and store images for IRC review
Saliva for germline DNA (optional)	X								Collect only if patient has consented to collection and testing; refer to Laboratory Manual for details
Whole blood for correlative studies		X		C2D1 and C4D1		X		X (Upon confirmation of PD)	- Samples to be provided for exploratory biomarker analyses (Section 8.10.5); refer to Laboratory Manual for details - If a patient discontinues treatment for reasons other than PD, a sample of whole blood should be collected during follow up when PD is confirmed - At the time of bone marrow biopsy to confirm CR, an additional collection of whole blood is required for exploratory biomarker analyses
Bendamustine administration – IV		90 mg/m ²	90 mg/m ²	90 mg/m ²	90 mg/m ²				- C1D1 should occur within 7 business days after randomization; refer to Table 6.1 - Date of last dose and date of decision for end of treatment must be recorded in EDC

Schedule of Assessments for Arm B: Bendamustine plus Rituximab (BR)									
Study Period	Baseline	Study Treatment (Cycle = 28 days)				Post-Study Treatment Discontinuation			Instructions
Evaluation	Screening	Cycle 1		Cycles 2-6		EOT	SFU	LTFU	Patients will proceed to EOT after the Cycle 6 treatment
Visit Window	Up to 28 days	Day 1	Day 2	Day 1 (± 7 days)	Day 2	+ 7 Days of last dose or decision to terminate treatment	28 Days (+ 7 days) after last dose or decision to terminate treatment	Q16W for first 2 years (relative to C1D1) and Q24W thereafter (± 4 weeks)	An EOT assessment should occur within 7 days of last dose of study treatment or decisions to terminate study treatment.
Rituximab administration – IV		375 mg/m ²		500 mg/m ² Day 1 of Cycles 2-6					- C1D1 should occur within 7 business days after randomization; refer to Table 6.1 - Date of last dose and date of decision for end of treatment must be recorded in EDC
Concomitant medication									Refer to Section 6.5
Adverse events									- Collect SAEs from the time of ICF signing through SFU. SAEs that occur prior to the first dose are considered medical history unless the SAE develops or worsens due to study-related procedures - All SAEs that the Investigator considers related to the study drug occurring after the SFU must be reported to the Sponsor - All SAEs must be reported to Clinical Safety within 24 hours of knowledge of the event - Second primary malignancy (SPM) events will continue to be reported up to 5 years since the start of the treatment regardless of the seriousness or causal attribution to treatment (Section 8.6.6) - Collect AEs from the time of dosing through SFU

Schedule of Assessments for Arm B: Bendamustine plus Rituximab (BR)									
Study Period	Baseline	Study Treatment (Cycle = 28 days)				Post-Study Treatment Discontinuation			Instructions
Evaluation	Screening	Cycle 1		Cycles 2-6		EOT	SFU	LTFU	Patients will proceed to EOT after the Cycle 6 treatment
Visit Window	Up to 28 days	Day 1	Day 2	Day 1 (± 7 days)	Day 2	+ 7 Days of last dose or decision to terminate treatment	28 Days (+ 7 days) after last dose or decision to terminate treatment	Q16W for first 2 years (relative to C1D1) and Q24W thereafter (± 4 weeks)	An EOT assessment should occur within 7 days of last dose of study treatment or decisions to terminate study treatment.
Medical resources utilization									- Hospitalizations, emergency department visits, blood product transfusions, and hematopoietic growth factor use will be collected - Patients (on both treatment arms) need to be assessed Q16W for a total of 2 years, and then Q24W thereafter until PD or 48 months post C1D1 whichever occurs first
Patient reported outcomes									- Refer to Section 1.3.4 for details - Patients (on both treatment arms) need to be assessed according to Section 1.3.4 until PD or 48 months post C1D1 whichever occurs first
Survival status								X	- Survival information may be collected via telephone if no procedures are required. - Subsequent anticancer therapy information should be collected every 16 weeks for the first 2 years relative to C1D1 and approximately every 24 weeks thereafter until death or study completion

1.3.3. Schedule of Assessments for Optional Crossover Treatment (for patients crossing over from Arm B to Arm A)

This SoA is applicable only for patients who were initially randomly assigned to Arm B (BR), and who have PD that is confirmed by the IRC, and who are eligible for crossover (CO) treatment (refer to Section 5.3 Eligibility Criteria for Crossover Treatment), and have elected for optional crossover.

Patients who cross over will complete the Arm B EOT before crossing over to Arm A. Testing and assessments that are performed as part of Arm B, and that are within the Screening window of up to 42 days, do not need to be repeated as a part of the Screening evaluation for crossover.

Schedule of Assessments for Optional Crossover Treatment							
Study Period	Baseline	Study Treatment (Cycle = 28 days)		Post-Study Treatment Discontinuation			Instructions
Evaluation	CO-Screening	CO-Cycle 1	CO-Cycle 4 and higher	CO-EOT	CO-SFU	CO-LTFU	
Visit Window	Up to 42 days	Day 1	± 14 Days	+14 Days of last dose or decision to terminate treatment	28 Days (+ 7 days) after last dose or decision to terminate treatment	Q24W (relative to CO-C1D1) ± 4 Weeks	
Informed consent	X						
Physical examination	X	X	Q24W from CO-C1D1	X	X		- Complete PE includes height (only at Screening), weight, basic neurological examination and review of relevant symptoms at Screening (refer to Section 8.4.2) - Symptom-targeted PE should be limited to systems of primary relevance such as, cardiovascular, respiratory, and those associated with tumor assessment (lymph nodes, liver, and spleen) and may be performed at other timepoints; include weight as clinically indicated throughout the trial - Screening results obtained within 3 days of CO-C1D1 are acceptable as CO-C1D1 results

Schedule of Assessments for Optional Crossover Treatment						
Study Period	Baseline	Study Treatment (Cycle = 28 days)		Post-Study Treatment Discontinuation		
Evaluation	CO-Screening	CO-Cycle 1	CO-Cycle 4 and higher	CO-EOT	CO-SFU	CO-LTFU
Visit Window	Up to 42 days	Day 1	± 14 Days	+14 Days of last dose or decision to terminate treatment	28 Days (+ 7 days) after last dose or decision to terminate treatment	Q24W (relative to CO-C1D1) ± 4 Weeks
Instructions						
ECOG PS	X	X	Q24W from CO-C1D1	X	X	
Vital signs	X	X	Q24W from CO-C1D1	X	X	
Results of baseline tests in the section below are required for crossover eligibility determination						
12-lead ECG	X					
						- Obtain ECGs at specified visits and when patients are symptomatic. Refer to Section 8.4.4 - ECGs should be collected: - At Screening, triplicate ECG - If an unscheduled ECG is done at any time, an electrolyte panel (i.e., calcium, magnesium, and potassium) must be done to coincide with the ECG - If a clinically significant arrhythmia is detected, details must be entered in dedicated EDC pages
Hematology	X	X	Q24W from CO-C1D1	X	X	X
						- Includes hemoglobin, hematocrit, RBC count, WBC count, platelet count, percent or absolute differential (neutrophils, lymphocytes, basophils, eosinophils, and monocytes) - Screening results obtained within 3 days of CO-C1D1 are acceptable as C1D1 results - Refer to Section 10.2 Appendix 2 Clinical Laboratory Tests

Schedule of Assessments for Optional Crossover Treatment							
Study Period	Baseline	Study Treatment (Cycle = 28 days)		Post-Study Treatment Discontinuation			Instructions
Evaluation	CO-Screening	CO-Cycle 1	CO-Cycle 4 and higher	CO-EOT	CO-SFU	CO-LTFU	
Visit Window	Up to 42 days	Day 1	± 14 Days	+14 Days of last dose or decision to terminate treatment	28 Days (+ 7 days) after last dose or decision to terminate treatment	Q24W (relative to CO-C1D1) ± 4 Weeks	
Blood chemistries	X	X	Q24W from CO-C1D1	X	X		• Blood chemistry from serum or plasma should include assessment of: Sodium, potassium, chloride, glucose, creatinine, total protein, albumin, total bilirubin, ALT and AST • In addition, LDH, calcium, magnesium, phosphorus and uric acid are required at Screening and CO-C1D1 and CO-C7D1 • Screening results within 3 days of CO-C1D1 are acceptable as CO-C1D1 results • Direct (or indirect) bilirubin should be performed any time total bilirubin is abnormal • Refer to Section 10.2 Appendix 2 Clinical Laboratory Tests
Coagulation panel	X						• Screening and as clinically indicated, aPTT and PT (or INR) • Refer to Section 10.2 Appendix 2 Clinical Laboratory Tests
Serum or urine pregnancy test (WOCBP only)	X	X	Q24W from CO-C1D1				• Perform within 24 hours of first dose of study treatment, and as indicated in table, or as required per local regulations and/or institutional guidelines; refer to Section 10.3 Appendix 3 • Refer to Section 10.2 Appendix 2 Clinical Laboratory Tests
Urinalysis	X	As clinically indicated					• Dipstick analysis is acceptable and should include color, specific gravity, pH, glucose, bilirubin, occult blood, protein, leukocytes, and urobilinogen • Refer to Section 10.2 Appendix 2 Clinical Laboratory Tests
Documentation or sampling of the following are required during Screening, but results not required prior to initiation of pirtobrutinib							

Schedule of Assessments for Optional Crossover Treatment						
Study Period	Baseline	Study Treatment (Cycle = 28 days)		Post-Study Treatment Discontinuation		
Evaluation	CO-Screening	CO-Cycle 1	CO-Cycle 4 and higher	CO-EOT	CO-SFU	CO-LTFU
Visit Window	Up to 42 days	Day 1	± 14 Days	+14 Days of last dose or decision to terminate treatment	28 Days (+ 7 days) after last dose or decision to terminate treatment	Q24W (relative to CO-C1D1) ± 4 Weeks
Instructions						
CT or MRI	X		Q24W from CO-C1D1	X		X
Pirtobrutinib administration						
Patient dosing diary						
Concomitant medication						

- Refer to Section 8.3.1 for details.
- If baseline CT or MRI assessment documenting PD by IRC was performed within 42 days of planned CO-C1D1, a new scan does not need to be obtained
- All response assessments should occur at Q24W intervals relative to CO-C1D1 regardless of any treatment delays or interruptions
- Investigator assessment of CT or MRI will be done locally at frequency of at least every 24 weeks or based on standard of care

- 200 mg PO administered QD (continuous); refer to Table 6.1
- Crossover treatment should be initiated within a window of 42 days after the IRC-confirmed PD
- Patient to visit study site Q12W from CO-C4D1 for dispensation of pirtobrutinib
- Date of last dose of BR regimen and date of decision to end treatment must be recorded in EDC prior to patient receiving first dose of treatment in crossover

Refer to Section 6.5

Schedule of Assessments for Optional Crossover Treatment						
Study Period	Baseline	Study Treatment (Cycle = 28 days)		Post-Study Treatment Discontinuation		
Evaluation	CO-Screening	CO-Cycle 1	CO-Cycle 4 and higher	CO-EOT	CO-SFU	CO-LTFU
Visit Window	Up to 42 days	Day 1	± 14 Days	+14 Days of last dose or decision to terminate treatment	28 Days (+ 7 days) after last dose or decision to terminate treatment	Q24W (relative to CO-C1D1) ± 4 Weeks
Instructions						
Adverse events						- Collect SAEs from the time of ICF signing through CO-SFU. SAEs that occur prior to the first dose are considered medical history unless the SAE develops or worsens due to study-related procedures - All SAEs that the Investigator considers related to the study drug occurring after the CO-SFU must be reported to the Sponsor - All SAEs must be reported to Clinical Safety within 24 hours of knowledge of the event - Collect AEs from the time of dosing through CO-SFU
Survival status						- Survival information may be collected via telephone if no procedures are required. This information should be collected approximately every 24 weeks relative to CO-C1D1; refer to Section 8.3 - Subsequent anticancer therapy information should be collected every 24 weeks relative to CO-C1D1 until death or study completion

1.3.4. Schedule of Assessments for Patient Reported Outcomes, Arms A and B

Instrument	Cycle 1	Completed at Home ^a until PD or until 4 years (48 months) post C1D1, whichever occurs first (for both arms)			Instructions
		Cycles 2 thru 8 (±7 Days) Every 4 weeks	Cycles 2 thru 8 (±7 Days) Every 8 weeks	Cycle 9+ ^c (+21 Days) Every 16 weeks for first 2 years and every 24 weeks thereafter	
EORTC QLQ-C30	X		X	X	The patient will complete all PRO assessments at home using the provided electronic device except for baseline (C1D1) which patients will complete at clinic. PRO assessments administered at clinic on C1D1 must be completed prior to first dose of study drug.
EORTC IL58 (CLL/SLL Symptoms Supplement)	X		X	X	
EORTC IL19 (Physical Function)		X ^b			
EORTC IL87 (CLL/SLL Symptom Assessment)		X ^b			
PGIS	X	X		X	
PGIC		X		X	
EQ-5D-5L	X		X	X	

a All evaluations completed via electronic Patient Reported Outcome (ePRO) device.

b This instrument not administered on weeks where the EORTC QLQ-C30 and EORTC IL58 are administered due to overlapping items.

c At Cycle 9, ePRO assessments will align as much as possible with the efficacy assessments (i.e., Q16W for the first 2 years and Q24W thereafter).
ePRO assessments will continue until PD or until 4 years (48 months) post C1D1, whichever occurs first (for both arms).

2. INTRODUCTION

2.1. Study Rationale

Pirtobrutinib is an orally available, highly selective, ATP-competitive inhibitor of BTK distinct from the approved BTK inhibitors (ibrutinib, acalabrutinib, and zanubrutinib) on the basis of its selectivity, favorable pharmacologic and PK properties, and non-covalent binding mode ([Brandhuber et al. 2018](#)). In a Phase 1/2 study (LOXO-BTK-18001, NCT03740529), pirtobrutinib has demonstrated robust and durable anti-tumor activity against a variety of B-cell malignancies including CLL/SLL, regardless of prior treatment and including in patients previously treated with covalent BTK inhibitors.

The proposed Phase 3 study is a global, randomized, open-label study in patients with previously untreated CLL/SLL with no evidence of 17p deletion who require therapy per iwCLL 2018 criteria, to assess the superiority of pirtobrutinib to BR. The proposed study will evaluate the role of non-covalent BTK inhibitor therapy in a prospectively identified CLL/SLL population of patients who are treatment naïve.

2.2. Background

BTK is a member of the TEC family of non-receptor tyrosine kinases (which includes BTK, ITK, TEC, TXK, and BMX) and a key component of the B-cell receptor (BCR) signaling complex. BTK also plays a critical role in the proliferation and survival of diverse B-cell malignancies.

BTK inactivating mutations were originally identified as the cause of X-linked immunodeficiency (Xid) in mice ([Rawlings et al. 1993](#), [Thomas et al. 1993](#)) and X-linked agammaglobulinemia (XLA) in humans ([Vetrie et al. 1993](#)). XLA is a rare, X-linked recessive disorder that causes severe bacterial infections in affected boys due to a complete absence of functional B lymphocytes and antibodies ([Hendriks et al. 2011](#)). Lifelong treatment with antibiotic prophylaxis and IV and/or subcutaneous (SC) immunoglobulins can prevent infection and lead to normal life expectancy.

In normal B cells, antigen binding to the BCR leads to activation of the upstream kinases LYN and SYK, recruitment of PI3K, generation of the second messenger PIP3 and PIP3-dependent recruitment of BTK to the plasma membrane. LYN and SYK-mediated phosphorylation of BTK on tyrosine residue 551 (Y551) stimulates the kinase activity of BTK, leading to autophosphorylation on Y223 and phosphorylation-dependent activation of the critical downstream signaling effector phospholipase C gamma 2 (PLCg2). PLCg2-mediated generation of second messengers inositol 3-phosphate and diacyl glycerol induces the activation of several critical signaling effectors (nuclear factor of activated T cells [NFAT], mitogen-activated protein kinase [MAPK]/extracellular signal-regulated kinase [ERK], protein kinase C [PKC], nuclear factor kappa-light-chain-enhancer of activated B-cells [NF-kB]) which results in increased proliferation and survival.

BTK expression is restricted to a subset of B-cells and myeloid cells, and in malignancies thought to derive from them, including CLL (related to naïve B-cells), MCL and marginal zone lymphoma (MZL, each related to germinal center B-cells) and Waldenström's macroglobulinemia (WM, plasma cells). Consistent with a critical survival role for BTK in these malignancies, BTK deficiency abrogates tumor formation in CLL mouse models (Kil et al. 2013), and treatment of primary, patient-derived CLL, MCL, and WM cells, with the irreversible BTK inhibitor ibrutinib reduces their viability, adhesion and migration (Herman et al. 2011, Chang et al. 2013, Yang et al. 2013).

Three BTK inhibitors are now approved for the treatment of patients with B-cell malignancies. These agents have altered the treatment paradigms for many B-cell malignancies, including CLL/SLL (ibrutinib, acalabrutinib, and zanubrutinib), relapsed/refractory (r/r) MCL (ibrutinib, acalabrutinib, and zanubrutinib), WM (ibrutinib and zanubrutinib), and MZL (ibrutinib and zanubrutinib). These agents potently inhibit BTK by binding to the ATP pocket of the enzyme and forming an irreversible, covalent bond with the C481 in the BTK enzyme. Covalent ligation of BTK inhibits its kinase activity, induces BTK degradation and causes potent and prolonged BTK target engagement and inhibition in patients (Byrd et al. 2013, Byrd et al. 2016). Treatment with other, investigational irreversible BTK inhibitors has produced near total BTK suppression in circulating leukemia cells and lymphoma/leukemia lymph node reservoirs and induced significant tumor responses (Tam et al. 2015). However, ibrutinib, acalabrutinib, and zanubrutinib are covalent BTK inhibitors with limited oral bioavailability, high protein binding, and half-lives that are significantly shorter than their dosing intervals. The clinical efficacy of these agents is therefore attributed to their irreversible binding mode at the C481. Once bound to BTK, these agents require protein turnover to “undo” their pharmacodynamic effects of inhibition. Reliance on covalent binding may lead to diminished target coverage towards the end of the dosing interval (i.e., low trough coverage) and to diminished target coverage in rapidly proliferating tumors with higher BTK protein turnover with subsequent loss of clinical activity.

Although irreversible BTK inhibitors have transformed the treatment of several B-cell malignancies, their long-term efficacy is ultimately limited by toxicity and acquired resistance. In r/r CLL, although initial response rates to ibrutinib are high, rates of treatment discontinuation are also high (~40%) with extended follow-up (Woyach et al. 2017, Mato et al. 2018). The most common reasons for treatment discontinuation are adverse events (AEs) in ~50 to 60%, CLL progression in ~20 to 30%, and Richter's Transformation in ~5 to 15% of patients. Toxicities of ibrutinib that lead to dose interruptions and treatment discontinuation include arthralgia, atrial fibrillation, rash, cytopenias, infection, pneumonitis, bleeding and diarrhea (Mato et al. 2018). These toxicities have been attributed to both on-target BTK inhibition and off-target inhibition of other kinases such as TEC (McMullen et al. 2014, Kamel et al. 2015). Acalabrutinib, which is more selective than ibrutinib against non-BTK kinase off-targets in preclinical studies, has been associated with a lower overall frequency of some (e.g., atrial fibrillation, major bleeding), but not other (e.g., cytopenias, upper respiratory infection, diarrhea) toxicities in clinical trials (Byrd et al. 2013, Byrd et al. 2016). A retrospective analysis of the RESONATE study indicated worse PFS in patients with r/r CLL with lower ibrutinib dose intensity and dose interruptions

lasting for longer than 7 days, suggesting that treatment interruptions for toxicity can adversely impact long-term outcomes (Barr et al. 2017).

Recent analysis of primary CLL samples from patients with relapsed CLL who responded to, but then ultimately progressed on ibrutinib, has uncovered two primary mechanisms of acquired resistance: substitution at C481, primarily with a serine residue (i.e., C481S) in the majority (67%) of patients, which prevent irreversible binding of ibrutinib (and acalabrutinib) to BTK; activating mutations in PLCγ2, a critical signaling effector downstream of BTK in 13%; and less commonly, both mutations occurring in the same patient (7%) (Woyach et al. 2017). These frequencies have been validated in more recent studies (Bonfiglio et al. 2018). Other studies have uncovered C481 substitution mutations in WM and MCL, indicating that C481 substitutions represent a common mechanism of “on-target” resistance to irreversible BTK inhibitors in patients (Chiron et al. 2014; Xu et al. 2017). C481 substitutions prevent irreversible ligation of ibrutinib (and other irreversible BTK inhibitors) to BTK. These mutations lead to insufficient BTK target coverage in patients and treatment failure as a result (Byrd et al. 2013; Woyach et al. 2017).

2.2.1. Current Approaches to Initial Therapy of CLL/SLL

CLL/SLL is the most common form of adult leukemias in the Western world and accounts for approximately 30-40% of all leukemias (Wierda et al. 2020; Eichhorst et al. 2015). SLL defines the same disease manifesting predominantly in lymph nodes instead of as leukemia. The median age at diagnosis has variously been reported as between 67 and 72 years of age with male predominance (Watson et al. 2008; Review of Cancer Medicines on the World Health Organization [WHO] List of Essential Medicines 2014). CLL/SLL occurs in approximately 3.8-4.2 in 100,000 people in the EU (Sant et al. 2010; Eichhorst et al. 2015) and 4.5 in 100,000 people per year in the US (Howlader et al. 2020). Allogeneic stem cell transplantation is the only known curative therapy, but with limited applicability to the typical patient diagnosed with CLL/SLL who generally is older with co-morbidities. Thus, treatment is not given with intent to cure and while many patients do not need treatment at diagnosis, once initiated, sequential treatments are the standard to extend survival. Ongoing efforts to identify therapies which can contribute to the meaningful improvement of patient outcomes are needed.

The treatment landscape for patients with CLL/ SLL has evolved over the last 10 years, resulting in markedly improved long-term outcomes (Burger 2020). While CIT had formed the foundation of therapy, more recent insights into the biologic dependence of CLL/SLL on B-cell receptor signaling, as well as anti-apoptotic machinery has led to the successful development of several novel targeted therapies, including agents inhibiting the BTK, BCL2, and PI3K delta. The introduction of these novel agents, in both, treatment naïve and previously treated patients has significantly improved the outcome of patients with CLL (Fischer et al. 2019; Shanafelt et al. 2019; Woyach et al. 2018; Burger et al. 2015). When making treatment decisions, several factors are considered. The covalent BTK inhibitors are given continuously to maximize the therapeutic effect. Additionally, ibrutinib, which is the widely available covalent BTK inhibitor, is less selective against BTK and therefore, exhibits a toxicity profile beyond on-target

effect that leads to frequent treatment discontinuation. Further, venetoclax, a BCL2 inhibitor, is approved in certain regions in combination with obinutuzumab in the frontline setting, and with rituximab in patients with relapsed/refractory CLL/SLL. Venetoclax-based therapy can provide patients with the opportunity to receive time-limited therapy. However, venetoclax requires intense monitoring, and in some cases, hospitalization due to the risk of TLS and the need for prophylactic therapy and IV hydration.

While covalent BTK inhibitors and venetoclax-based regimens are increasingly utilized as initial therapy for patients with CLL/SLL, substantial heterogeneity in treatment patterns continue to exist both globally and in the US. Contemporary prescribing data from a prospective US-based registry of CLL/SLL patients illustrate this point ([Mato et al. 2020](#)). In this cohort of 1462 patients enrolled since 2015 (93% from community-based sites), 25% of treatment-naïve CLL/SLL patients who initiated treatment in 2019 received frontline CIT. These data, in addition to other prescribing databases, continue to support the assertion that while the uptake of CIT has declined since the approval of targeted therapies, CIT continues to represent a significant treatment option for this patient population. Of note, BR was the most frequently used CIT regimen in this registry in the frontline setting ([Mato et al. 2020](#)).

CIT has served as the foundation for treating patients with CLL/SLL for many years. These regimens were utilized based on several factors including patient age, performance status, comorbid conditions and the disease molecular features. FCR demonstrated significant activity against CLL/SLL, but was associated with significant toxicity including prolonged immune suppression, hence this regimen is reserved to minority of patients with CLL/SLL who are fit, with no significant comorbid conditions, and younger than age 65 years. The CLL10 study was a randomized Phase 3 study that compared BR to FCR in patients with CLL/SLL who were treatment naïve with no evidence of 17p deletion, and who required therapy per iwCLL 2008 ([Eichhorst et al. 2016](#)). After a median follow up of 58.2 months, the median PFS of patients treated with BR was 42.3 months. Five-year OS was not different between BR and FCR (80.1% versus 80.9% respectively). Treatment with FCR in patients > 65 years of age was associated with increased incidence of secondary malignancies (32.6% versus 16.8% in FCR versus BR) ([Kutsch et al. 2020](#)). This study established BR as the preferred regimen for patients > 65 years of age, or who are < 65 years of age but with comorbid conditions that deems FCR contraindicated. While the follow up is not as mature, the data from the Alliance study also demonstrated an estimated median PFS of 43 months for patients treated with BR. The Alliance study enrolled patients with CLL/SLL who are treatment naïve, but also included patients with evidence of 17p deletion (8% of patients treated with BR) ([Woyach et al. 2018](#)). In both of these studies (CLL10 and Alliance), BR provided the opportunity for time-limited therapy with durable disease control (estimated median PFS of 43 months) and improved treatment free intervals, which supports the ongoing use of BR in the US and globally in the frontline setting ([Eichhorst et al. 2016](#); [Woyach et al. 2018](#)).

These data underscore the fact that, despite the availability of targeted therapy in the front-line setting, a substantial minority of patients in the US continue to receive CIT in frontline setting. Several reasons make up the rationale for choosing BR:

- 1) BR continues to be utilized in clinical practice ([Mato et al. 2020](#)), and is recognized by National Comprehensive Cancer Network (NCCN) and European Society of Medical Oncology (ESMO) guidelines for frontline therapy,
- 2) BR is favored globally by treating physicians amongst CIT regimens due to its activity, and the option for time-limited therapy,
- 3) BR doesn't require dose escalation, hospitalization in high-risk patients, or intense monitoring for TLS, and
- 4) in several regions, targeted therapy such as covalent BTK inhibitors or venetoclax, are reserved for either high-risk disease (17 p deletion) in the frontline setting, or for patients with relapsed disease.

For the proposed Phase 3 study, the comparator arm will be bendamustine in combination with rituximab (BR) which is an established treatment option for patients with untreated CLL/SLL with no evidence of 17p deletion, and is recognized by NCCN and ESMO as a treatment option for patients with CLL/SLL ([Eichhorst et al. 2020](#); [Wierda et al. 2020](#)).

Benefit/Risk Assessment:

Pirtobrutinib has demonstrated clinical activity in the patient population specified for this study. Study LOXO-BTK-18001 (NCT03740529) is a first in human global Phase 1/2 study evaluating the safety and efficacy of pirtobrutinib in patients with CLL/SLL and B-cell NHL who have failed or are intolerant to standard of care therapy. The study commenced enrollment in March 2019 to establish the safety of pirtobrutinib, assess PK, identify a recommended Phase 2 dose (RP2D) and a maximal tolerated dose (MTD). During Phase 1 dose escalation, pirtobrutinib was well tolerated at dose levels of 25 mg to 300 mg once daily QD with no dose-limiting toxicities. Given the totality of efficacy, clinical PK, and safety data, the Sponsor and Safety Review Committee decided that ongoing dose escalation was not medically justified and therefore no MTD was established. A RP2D was identified as 200 mg orally (PO) QD.

PK data show that pirtobrutinib is absorbed after oral administration with a median time to maximum plasma concentration (T_{max}) of approximately 2 hours and low clearance. Plasma half-life appears to be approximately 20 hours. Steady-state area under the concentration versus time curve time 0 to 24 hours (AUC_{0-24}) increase in approximate proportion with daily dose. Following administration of 100 mg QD or higher, mean unbound trough plasma levels of pirtobrutinib exceeded the IC_{90} of BTK-wt and BTK C481S in vitro.

Efficacy data from the LOXO-BTK-18001 study show robust and durable anti-tumor activity against a variety of B-cell malignancies including pretreated CLL/SLL. Enrolled patients have varied prior therapies, including diverse combinations of chemotherapy, anti-CD20 antibodies, BCL2 inhibitors, PI3K inhibitors and BTK inhibitors. The vast majority of CLL/SLL patients

treated on the LOXO-BTK-18001 study received a prior BTK inhibitor. Anti-tumor activity has been seen in the majority of patients, regardless of prior treatment, including in patients treated with covalent BTK inhibitors. Of note, durable objective responses have been seen in patients with acquired resistance to prior BTK therapy, regardless of BTK C481 mutational status.

Safety data are available from a total of 330 patients treated in Phase 1/2 Study LOXO-BTK-18001. This includes 324 patients treated at doses ranging from 25 mg QD to 300 mg QD in Phase 1/2 Monotherapy cohorts, and 6 patients treated in Phase 1b Combination Arm A (pirtobrutinib 200 mg QD plus venetoclax 400 mg QD [after ramp-up according to prescribing information]). The majority of treated patients were patients with CLL/SLL (176 patients, 52.9%; this includes the 6 patients enrolled in Phase 1b Combination Arm A) or MCL (61 patients, 18.8%). Treatment-emergent adverse events (TEAEs) were reported in 268 of the 330 treated patients (81.2%) treated in the study.

In the 324 patients in the Phase 1/2 Monotherapy cohorts in Study LOXO-BTK-18001, TEAEs reported in $\geq 10\%$ of patients ($n = 33$ or more) were fatigue (20.1% total, 8.3% related), diarrhea (17.0% total, 8.6% related), and contusion (13.0% total, 9.0% related). Drug-related TEAEs were reported in 156 of 324 patients (48.1%) in the Phase 1/2 Monotherapy cohorts; the most frequently reported drug related TEAEs for pirtobrutinib (those in $> 5\%$ of patients overall) were contusion (9.0%), diarrhea (8.6%), and fatigue (8.3%). All other drug related TEAEs were reported in $< 5\%$ of patients (i.e., < 17 patients each). TEAEs of severity Grade 3 or 4 were reported in 87 of 324 of patients (26.9%) in the Phase 1/2 Monotherapy cohorts, with 41 (12.7%) of these Grade 3 or 4 AEs reported as related to study drug. On-study death (death within 28 days of the last dose of study) due to a Grade 5 (fatal) TEAE was reported in 4 of 324 patients (1.2%) in the Phase 1/2 Monotherapy cohorts. One of the Grade 5 AEs, *Enterococcus faecium* related septic shock, was considered to be related to study drug; this patient had multiple underlying concomitant risk factors; including underlying disease, recent splenectomy prior to enrollment and 11 prior lines of therapy; while the Investigator did not deem pirtobrutinib directly causative, study drug was believed to be contributory to the event severity.

In Phase 1b Combination Arm A of Study LOXO-BTK-18001, TEAEs were reported in 3 of the 6 patients treated; no TEAE was reported more than once, and all TEAEs were Grade 1 or 2. Study drug-related TEAEs were reported in 2 of 6 patients In Phase 1b Combination Arm A; these included: Grade 1 contusion, diarrhea, fatigue, blood alkaline phosphatase increased, abdominal distension; and Grade 2 neutrophil count decreased. In the Phase 1b Combination Arm A, no TEAEs of Grade 3 or higher were reported.

The safety profile in Study LOXO-BTK-18001 is reflective of the selectivity of pirtobrutinib. Additional information about the known and expected risks, serious adverse events (SAEs), and reasonably anticipated AEs of pirtobrutinib, is provided in the pirtobrutinib Investigator's Brochure (IB).

The Sponsor plans to compare pirtobrutinib to BR, an established front line treatment option that is recognized by NCCN/ESMO and utilized globally in first line setting in patients with untreated CLL/SLL with no evidence of 17p deletion ([Eichhorst et al. 2020](#); [Wierda et al. 2020](#)).

Overall Benefit/Risk Conclusion:

During the Phase 1/2 study, pirtobrutinib has demonstrated a favorable safety profile and positive efficacy. Additionally, considering the measures taken to ensure the participants in this study are safe, the potential risks from taking part in the study are justified by the potential benefits for individuals with chronic lymphocytic leukemia/small lymphocytic lymphoma.

3. OBJECTIVES AND ENDPOINTS

Table 3.1 Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate PFS of pirtobrutinib as monotherapy (Arm A) compared to BR (Arm B).	Assessed by IRC: PFS per iwCLL 2018 response criteria
Secondary	
To evaluate the effectiveness of Arm A compared to Arm B based on ORR and time to event(s) outcomes	- Assessed by Investigator: - PFS per iwCLL 2018 criteria - OS - TTNT, defined as time from the date of randomization to the date of the next systemic anticancer therapy for CLL/SLL (see Section 9 for full definition). - Assessed by Investigator and IRC: - ORR - DOR
To evaluate the safety and tolerability of each treatment arm	Including, but not limited to, serious adverse events (SAEs), adverse events (AEs), deaths, and clinical laboratory abnormalities per National Cancer Institute Common Terminology Criteria for Adverse Events v5.0 (NCI CTCAE v5.0)
To evaluate the effectiveness of Arm A compared to Arm B based on patient reported outcomes	- Patient reported outcomes of: - TTW of CLL/SLL-related symptoms - TTW of physical functioning as measured by the physical function domain of the EORTC-QLQ-C30
Tertiary or Exploratory Objectives	
- To identify biomarkers of response and survival in patients treated in both study arms - To identify mechanisms of resistance to pirtobrutinib - To assess use of medical resources including hospitalizations and emergency department visits, transfusions, and growth factor support according to treatment arm - To explore the relationship between pirtobrutinib plasma exposure and selected efficacy and safety outcomes - To compare HRQoL measured by EORTC QLQ-C30 and EQ-5D-5L between the treatment arms	

4. STUDY DESIGN

4.1. Overall Design

LOXO-BTK-20023 (BRUIN-CLL-313) is a Phase 3 global, randomized, open-label study comparing pirtobrutinib as continuous monotherapy (Arm A) to BR (Arm B) in patients with untreated CLL/SLL with no evidence of 17p deletion. The Study Schematic is provided in Section 1.2. Eligible patients will be randomized in 1:1, Arm A:Arm B, based on stratification factors of IGHV mutation status (mutated versus unmutated), and Rai stage (low/intermediate versus high).

This study will enroll adult CLL/SLL patients with an indication for treatment as defined by iwCLL 2018 criteria (Section 10.7, Appendix 7). Patients assigned to oral pirtobrutinib will receive this continuously until discontinuation criteria are met (Section 7). Patients assigned to BR will receive up to 6 cycles of both agents intravenously and then be followed until progression, death, lost-to follow-up, withdrawal of consent, or study completion. Patients randomly assigned to Arm B will be allowed to cross over to Arm A upon confirmation of PD by IRC and if they meet the eligibility criteria for crossover (Section 5.3). Patients who discontinue treatment for any reason other than PD, death, lost to follow-up, or withdrawal of consent will be followed for tumor assessment until PD, regardless of whether the patient receives a new anticancer therapy.

4.2. Scientific Rationale for Study Design

This study will compare the efficacy and safety in of pirtobrutinib administered as a continuous monotherapy with BR. The patient population will encompass patients with untreated CLL/SLL with no evidence of 17p deletion who require therapy per iwCLL 2018 criteria. The study will aim to establish the superiority and favorable safety profile of pirtobrutinib over BR, an established treatment option and a relevant global standard for frontline therapy, in patients with no evidence of 17p deletion.

4.3. Justification for Dose

4.3.1. Pirtobrutinib

Preclinical data supporting the selection of the starting dose of pirtobrutinib for the first-in-human Phase 1/2 study of pirtobrutinib (LOXO-BTK-18001) is provided in the pirtobrutinib IB. During Phase 1 dose escalation, pirtobrutinib has been administered at doses ranging from 25 mg QD to 300 mg QD. Response was seen at all dose levels including 25 mg QD and across tumor types. PK data obtained during dose escalation demonstrated that at doses of 100 mg QD or higher, mean trough plasma levels of pirtobrutinib exceeded the concentration required for 90% inhibition ($IC_{90} = 825 \text{ ng/mL}$) of BTK in vitro. During Phase 1, additional patients were enrolled to dose levels cleared for safety to confirm safety and evaluate additional preliminary efficacy. In May 2020, based on the totality of PK, safety, and clinical data in Study LOXO-BTK-18001, the Sponsor and Safety Review Committee (SRC) identified the recommended Phase 2 dose

(RP2D) of pirtobrutinib as 200 mg QD. As of 27 September 2020, 330 patients had been dosed with pirtobrutinib in Study LOXO-BTK-18001, and a starting dose of 200 mg QD was administered to 239 of the 324 (73.8%) treated patients in the Phase 1/2 monotherapy cohorts, and to all of the 6 patients treated in Phase 1b combination arm (pirtobrutinib plus venetoclax).

4.3.2. Bendamustine plus Rituximab (BR)

Bendamustine should be given at 90 mg/m² IV on Days 1 and 2 of Cycles 1 through 6. The rationale for using 90 mg/m² is based on the established tolerated dose of bendamustine with rituximab in patients with CLL treated in the frontline setting, which has been evaluated in two randomized Phase 3 clinical trials, CLL10 and Alliance study A041202 ([Eichhorst et al. 2016](#); [Woyach et al. 2018](#)).

Rituximab should be administered at 375 mg/m² for the first cycle and then 500 mg/m² on Day 1 of Cycles 2 through 6. Premedication may be required for rituximab and should be administered per local institutional standard. Biosimilar anti-CD20 is permitted in accordance with local prescribing practice. Subcutaneous formulation or administration of rituximab is not be allowed. Rituximab as IV push or bolus administration will not be allowed. Patients should receive the same formulation throughout the duration of the trial (either branded or biosimilar).

Study drug administration details are provided in Section 6.1. Dose modifications for toxicities are detailed in Section 6.6.

4.4. End of Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in the SoA for the last participant in the trial globally, which is estimated at approximately 52 months from the first patient randomized.

5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Patients are eligible to be included in the study only if all of the following criteria apply:

Age

1. Age 18 years or older per local regulations at time of enrollment.

Type of Patient and Disease Characteristics

2. Confirmed diagnosis by redacted local laboratory report of CLL/SLL as defined by iwCLL 2018 criteria including the following:
 - a) B cells must:
 - (1) co-express CD5 and CD23
 - (2) express at least one B cell antigen (CD19 or CD20), and
 - (3) be either κ or λ light-chain restricted.

Atypical cases may be considered with Sponsor approval.

 - b) $\geq 5 \times 10^9$ B lymphocytes/L (5000/ μ L) in the peripheral blood for CLL patients. For SLL patients, $< 5 \times 10^9$ B lymphocytes/L (5000/ μ L) in the peripheral blood is allowed.
 - c) Prolymphocytes may comprise $\leq 55\%$ of blood lymphocytes (for CLL patients).
3. A requirement for therapy consistent with iwCLL 2018 criteria for initiation of therapy such that at least 1 of the following should be met:
 - a) Evidence of progressive marrow failure as manifested by the development of, or worsening of, anemia (such as hemoglobin < 10 g/dL) and/or thrombocytopenia (such as platelets $\leq 100 \times 10^9$ /L).
 - b) Massive (i.e., spleen edge ≥ 6 cm below the left costal margin) or progressive or symptomatic splenomegaly (> 13 cm).
 - c) Massive nodes (i.e., ≥ 10 cm in longest diameter) or progressive or symptomatic lymphadenopathy.
 - d) Progressive lymphocytosis with an increase of $> 50\%$ over a 2-month period, or lymphocyte doubling time < 6 months. Factors contributing to lymphocytosis other than CLL/SLL (e.g., infections, steroid administration) should be excluded.
 - e) Autoimmune complications including anemia or thrombocytopenia poorly responsive to corticosteroids.
 - f) Symptomatic or functional extranodal involvement (e.g., skin, kidney, lung, spine).

- g) Disease-related symptoms (also known as B-symptoms) as defined by any of the following:
- i) Unintentional weight loss $\geq 10\%$ within the previous 6 months.
 - ii) Significant fatigue (i.e., Eastern Cooperative Oncology Group [ECOG] performance scale 2 or worse; cannot work or unable to perform usual activities).
 - iii) Fevers $\geq 100.5^{\circ}\text{F}$ or 38.0°C for 2 or more weeks without evidence of infection.
 - iv) Night sweats for ≥ 1 month without evidence of infection.
4. Eastern Cooperative Oncology Group (ECOG) 0-2.
5. Must have adequate organ function, as defined below. Results from the most recent laboratory tests prior to enrollment will be used for eligibility.

System	Laboratory Value
Adequate Bone Marrow Function	
Absolute neutrophil count (ANC)	$\geq 0.75 \times 10^9/\text{L}$ without granulocyte-colony-stimulating factor (GCSF) support
Platelets	$\geq 75 \times 10^9/\text{L}$ not requiring transfusion support or growth factors within 14 days of C1D1. ($\geq 50 \times 10^9/\text{L}$ for patients with evidence of bone marrow infiltrate or are screening for crossover from Arm B to Arm A)
Hemoglobin	$\geq 8 \text{ g/dL}$ not requiring transfusion support or growth factors within 14 days of C1D1
Note: Patients who are receiving transfusions of blood or platelets for bone marrow involvement induced cytopenias, must be responsive to transfusion support. Patients refractory to transfusion support are not eligible. If the patient is cytopenic, there should be no evidence of myelodysplastic syndrome (MDS) or hypoplastic bone marrow.	
Hepatic	
Total bilirubin	$\leq 1.5 \times$ upper limit of normal (ULN) or $\leq 3 \times$ ULN if with documented liver involvement. If total bilirubin is $> 1.5 \times$ ULN the direct and/or indirect (or conjugated/unconjugated and/or unconjugated) bilirubin tests should be performed.
	Patients with Gilbert's Syndrome or hemolysis may be enrolled if indirect (unconjugated) bilirubin is $< 3 \times$ ULN (indirect bilirubin = total bilirubin - direct bilirubin)
Alanine aminotransferase (ALT) and Aspartate aminotransferase (AST)	$\leq 3.0 \times$ the ULN or $\leq 5 \times$ ULN with documented liver involvement
Renal	
Creatinine clearance	$\geq 40 \text{ mL/minute}$ Using Cockcroft/Gault Formula: $(140 - \text{age}) \times \text{body weight (kg)} \times 0.85$ (if female) serum creatinine (mg/dL) $\times 72$

6. Patients are required to have had the following washout periods prior to planned C1D1:
 - a) Palliative limited field radiation: 7 days
 - b) Broad field radiation ($\geq 30\%$ of bone marrow or whole brain radiotherapy): 28 days

Contraception

7. Willingness of women of childbearing potential (WOCBP), and their partners, to both observe barrier method and highly effective birth control methods as outlined in Section 10.3 (Appendix 3 and below) for the duration of treatment and for 1 month following the last dose of pirtobrutinib or 12 months after the last dose of rituximab, whichever is later.

WOCBP are defined as women following menarche, and who are not postmenopausal (or 2 years of non-therapy-induced amenorrhea, or surgically sterile). WOCBP must utilize 2 effective contraception methods with at least 1 form of highly effective contraception method as outlined below. In addition, male partners must use a barrier method (condoms) for the duration of treatment and for 1 month following the last dose of study treatment or 12 months after the last dose of rituximab.

Male patients enrolled in Arm B with partners who are WOCBP must use a barrier method (condoms) and their partner must also use a highly effective form of contraception as listed below for the duration of treatment and for 12 months after the last dose of rituximab.

Highly effective birth control methods with a failure rate of less than 1% per year when used consistently and correctly are recommended (Clinical Trial Facilitation Group [CTFG 2014]):

- a. Combined estrogen and progestin containing hormonal contraception associated with inhibition of ovulation given orally, intravaginally, or transdermally
- b. Progestin-only hormonal contraception associated with inhibition of ovulation given orally, by injection, or by implant
- c. Intrauterine device (IUD)
- d. Intrauterine hormone-releasing system (IUS)
- e. Bilateral tubal occlusion
- f. Vasectomized partner
- g. Sexual abstinence: Considered a highly effective method only if defined as refraining from heterosexual intercourse during an entire period of risk associated with the study treatment. The reliability of sexual abstinence will be evaluated in relation to the duration of the study and to the usual lifestyle of the patient.

Notes:

- Women with a history of breast cancer may not use hormone containing contraception (a, b, or d). One of the other listed methods above should be selected.
- Women of childbearing potential using hormonal contraception methods should also use a barrier method as a second form of contraception.

Informed Consent

8. Willing and capable of giving signed informed consent as described in Section 10.1.2 Appendix 1 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

Other Inclusions

9. Able to swallow oral study medication.
10. Able to comply with outpatient treatment, laboratory monitoring, and required clinic visits for the duration of study participation.

5.2. Exclusion Criteria

Patients are excluded from the study if any of the following criteria apply:

Medical Conditions

1. Known or suspected Richter's transformation to diffuse large B-cell lymphoma (DLBCL), prolymphocytic leukemia, or Hodgkin lymphoma at any time preceding enrollment.
2. Presence of 17p deletion by fluorescence in-situ hybridization (FISH) (refer to Section 8.10.2)
3. Known or suspected history of central nervous system (CNS) involvement by CLL/SLL.
4. Active second malignancy. Patients with treated second malignancy who are in remission with life expectancy > 2 years and with documented Sponsor approval are eligible. Examples include:
 - a) Adequately treated non-melanomatous skin cancer or lentigo maligna melanoma without current evidence of disease.
 - b) Adequately treated cervical carcinoma in situ without current evidence of disease.
 - c) Localized (e.g., lymph node negative) breast cancer treated with curative intent with no evidence of active disease present for more than 3 years and receiving adjuvant hormonal therapy.
 - d) Localized prostate cancer undergoing active surveillance.
 - e) History of treated and cured Hodgkin's disease or NHL within 5 years from diagnosis.
5. Major surgery, within 4 weeks of planned start of study treatment.
6. A significant history of renal, neurologic, psychiatric, endocrine, metabolic or immunologic, that, in the opinion of the Investigator, would adversely affect the patient's participation in this study or interpretation of study outcomes.
7. Active uncontrolled auto-immune cytopenia (e.g., autoimmune hemolytic anemia [AIHA], idiopathic thrombocytopenic purpura [ITP]) not on a stable regimen and dose for at least 4 weeks prior to study enrollment

8. Significant cardiovascular disease defined as any of the following:
 - a) Unstable angina or acute coronary syndrome within the past 2 months,
 - b) History of myocardial infarction within 3 months prior to planned start of study drug,
 - c) Documented LVEF by any method of $\leq 40\%$
 - d) $\geq$ Grade 3 NYHA functional classification system of heart failure, uncontrolled or symptomatic arrhythmias
9. Prolongation of the QT interval corrected (QTc) for heart rate using Fredericia's Formula (QTcF) > 470 msec on at least 2 of 3 consecutive ECGs, and mean QTcF > 470 msec on all 3 ECGs, during Screening.
 - a) QTcF is calculated using Fredericia's Formula ($QTcF = QT/(RR^{0.33})$)
 - b) Correction of suspected drug-induced QTcF prolongation or prolongation due to electrolyte abnormalities can be attempted at the Investigator's discretion, and only if clinically safe to do so with either discontinuation of the offending drug or switch to another drug not known to be associated with QTcF prolongation or electrolyte supplementation.
 - c) Correction of QTc for underlying bundle branch block (BBB) permissible.
10. Hepatitis B or hepatitis C testing indicating active/ongoing infection based on Screening laboratory tests as defined as:
 - a) Hepatitis B virus (HBV): Patients with positive hepatitis B surface antigen (HBsAg) are excluded. Patients with positive hepatitis B core antibody (anti-HBc) and negative HBsAg require hepatitis B polymerase chain reaction (PCR) evaluation before randomization. Patients who are hepatitis B PCR positive will be excluded.
 - b) Hepatitis C virus (HCV): positive hepatitis C antibody. If positive hepatitis C antibody result, patient will need to have a negative result for hepatitis C ribonucleic acid (RNA) before randomization. Patients who are hepatitis C RNA positive will be excluded.
 - c) For optional crossover, repeat testing is not required.
11. Active cytomegalovirus (CMV) infection.
12. Evidence of other clinically significant uncontrolled condition(s) including, but not limited to, uncontrolled systemic infection (viral, bacterial, or fungal) or other clinically significant active disease process which in the opinion of the Investigator and Medical Monitor may pose a risk for patient participation. Screening for chronic conditions is not required.
13. Known Human Immunodeficiency Virus (HIV) infection, regardless of CD4 count. Patients with unknown or negative status are eligible.
14. Clinically significant active malabsorption syndrome or other condition likely to affect gastrointestinal (GI) absorption of the oral administered study treatments.

Prior/Concomitant Therapy

15. Prior systemic therapy for CLL/SLL (except palliative steroids or treatment of autoimmune complications of CLL with rituximab, rituximab biosimilar, or steroids)

16. Concurrent use of investigational agent or anticancer therapy except hormonal therapy.
17. Patients requiring therapeutic anticoagulation with warfarin or another Vitamin K antagonist.
18. Use of >20 mg prednisone QD or equivalent dose of steroid per day at the time of C1D1.
Patients may not be on prednisone of any dose intended for anti-neoplastic use.
19. Vaccination with a live vaccine within 28 days prior to randomization.

Other Exclusions

20. Are pregnant or intend to become pregnant or breastfeed during the study.
21. Patients with the following hypersensitivity:
 - a) Known hypersensitivity, including anaphylaxis, to any component or excipient of pirtobrutinib or bendamustine
 - b) Prior significant hypersensitivity to rituximab requiring discontinuation, prior allergic or anaphylactic reaction to rituximab (does not include manageable infusion related reaction)

5.3. Eligibility Criteria for Crossover Treatment

Patients who are randomly assigned to Arm B, may be eligible to cross over to Arm A treatment if they meet the following criteria:

- a) IRC-confirmed PD according to iwCLL 2018 criteria while on or after study treatment (Section 10.7, Appendix 7)
- b) Have not received any other anticancer systemic therapy from the time discontinued the control treatment
- c) Patients must meet inclusion and exclusion criteria detailed in Sections 5.1 and 5.2 (with the exception of exclusion criterion [15]), respectively, to be eligible for crossover to pirtobrutinib.

Once crossover eligibility is confirmed, the Schedule of Assessments for Optional Crossover Treatment (for patients crossing over from Arm B to Arm A) (Section 1.3.3) will be followed.

Patients who are eligible for crossover treatment will retain their assigned study number during crossover; i.e., patients will NOT be assigned a new study number.

5.4. Lifestyle Considerations

5.4.1. Meals and Dietary Restrictions

No food or drink restrictions are required for administration of pirtobrutinib.

Pirtobrutinib tablets should be swallowed whole.

5.5. Screen Failures

Repeat hematology and/or chemistry testing is permitted during the protocol-designated 28-day Screening Period and does not constitute rescreening. Results from the most recent hematology and/or chemistry tests during the Screening Period will be used for eligibility.

Screen failures are defined as patients who consent to participate in the clinical study, but are not subsequently randomized to a study treatment due to inability to complete or meet the criteria for participation (Sections 5.1 and 5.2). Rescreened patients must sign a new ICF and will be provided a new patient number with each rescreening. Rescreened patients may be required to repeat screening procedures and tests, with the exception of the bone marrow biopsy and aspirate (if collected within 90 days of randomization) and CT/MRI scan (if done within 42 days of randomization).

6. STUDY INTERVENTION

6.1. Study Interventions Administered

C1D1 (beginning of treatment administration) should occur within 7 business days after randomization. Treatment cycles will be 28 days.

Patients randomized to Arm A will receive treatment with pirtobrutinib monotherapy as outlined in [Table 6.1](#).

Patients randomized to Arm B will receive BR treatment with BR as outlined [Table 6.1](#). On days when bendamustine and rituximab are to be administered on the same day, rituximab will be administered prior to bendamustine.

Table 6.1 Intervention Groups and Duration

	Arm A pirtobrutinib	Arm B bendamustine plus rituximab (BR)	
Treatment	pirtobrutinib	bendamustine	rituximab
Dose	200 mg	90 mg/m ²	375 mg/m ² on C1D1 and then 500 mg/m ²
Schedule	QD in 28-day continuous cycles	90 mg/m ² on Day 1 and Day 2 of each 28-day cycle, Cycles 1 to 6	375 mg/m ² on C1D1 and then 500 mg/m ² given on Day 1 of each 28-day cycle, Cycles 2 to 6
Route	Oral	IV	IV
Authorized as defined by EU Clinical Trial Regulation	Authorized and not used according to EU authorization	Authorized and used according to EU authorization	Authorized and used according to EU authorization

Refer to local prescribing information for additional administration details for rituximab, or rituximab's approved biosimilar.

Packaging and labeling

Study interventions will be supplied by the sponsor or its designee in accordance with current Good Manufacturing Practice. Study interventions will be labeled as appropriate for country requirements.

6.1.1. Selection and Timing of Doses

A cycle is defined as an interval of 28 days during treatment period. The 28-day cycle length should be maintained throughout the treatment phase regardless of dose interruptions.

Patients will begin dosing assigned treatment on C1D1 or if crossover, on CO-C1D1. Treatment will continue until progression, unacceptable toxicity, or other reason for treatment discontinuation.

A delay for a maximum of 7 days of a cycle start not due to adverse event, but due to holiday, weekend, bad weather, or other unforeseen circumstances will be permitted and not counted as a protocol deviation. Response assessments should remain on the original schedule.

6.1.2. Arm A Pirtobrutinib: General Dosing Instructions

Each cycle will consist of 28 days. Pirtobrutinib will be given as 200 mg QD administered at approximately the same time on each day (refer to Section 6.1). Dosing of pirtobrutinib is intended to be fixed (i.e., not weight-based- or body surface area [BSA]-based).

Pirtobrutinib may be taken with food or drink. No fasting is required for pirtobrutinib. Refer to Section 6.5 and Section 10.5 Appendix 5 for concomitant medication considerations.

Patients randomized to pirtobrutinib treatment must keep a daily diary to record dosing compliance of oral study treatment, which will also be assessed at each clinic visit by means of a tablet count in the returned bottle(s). Late doses (i.e., 4 or more hours after scheduled time) should be noted in the diary. Doses that are late by more than 6 hours should not be made up and recorded in the dosing diary as missed. Reasons should be recorded for any missed dose. Vomiting after dosing should be noted in the diary and a vomited dose should not be re-dosed or replaced. Assessment of treatment compliance is described in Section 6.4.

Patients will continue pirtobrutinib dosing until PD, unacceptable toxicity, or other reason for treatment discontinuation. Patients who progress on Arm A, may be allowed to continue treatment beyond progression if the patient is tolerating study treatment and, in the opinion of the Investigator, is deriving ongoing clinical benefit. Patients considered for treatment beyond progression must not have symptomatic progression (examples include patients with progression based on lymphocytosis in the absence of evidence of bone marrow failure, or patients with isolated asymptomatic nodal progression). Continuation of treatment on Arm A post-progression must be approved by the Sponsor.

Effects of pirtobrutinib on coagulation are unknown. Thus, patients undergoing major surgical procedures should have pirtobrutinib held at least 3 days prior and 3 days post procedure; the Sponsor should be notified of the planned procedure and planned dose hold.

6.1.3. Arm B Bendamustine plus Rituximab (BR): General Dosing Instructions

Patients randomized to Arm B will begin dosing with BR on C1D1. Patients will be dosed as outlined above in Table 6.1. Handling of bendamustine and rituximab should be in accordance with instructions per locally approved labelling or institutional standards (US prescribing information is provided for reference: [Bendamustine USPI](#), [Rituximab USPI](#); [Rituximab biosimilars: Riabni™ USPI](#); [Ruxience™ USPI](#); [Truxima® USPI](#)). Refer to the local prescribing

information for additional dosing and administration details for rituximab or rituximab's approved biosimilar.

Rituximab should only be administered by a healthcare professional with appropriate medical support to manage severe infusion reactions that can be fatal if they occur.

Table 6.2 Specific Instructions for Bendamustine plus Rituximab (BR)

Drug	Administration
Bendamustine	- Bendamustine should be given IV at 90 mg/m² IV on Days 1 and 2 of Cycles 1 through 6. - On days when bendamustine and rituximab are to be administered, rituximab will be administered prior to bendamustine - The patient's BSA calculated at Screening should be used to calculate the dose of bendamustine throughout the study unless the patient's weight increases or decreases by > 10% from Screening. In obese patients, there is no cap on BSA and actual body weight, not adjusted weight, is recommended. Nonetheless, empiric dose adjustment is permitted in obese patients (obesity defined as body mass index ≥ 30 kg/m²). Patients will be dosed as outlined in as outlined above in Table 6.1 (Eichhorst et al. 2020; Wierda et al. 2020). Avoid inducers or inhibitors of CYP1A2.
Rituximab^a	- Rituximab will be infused IV at a dose of 375 mg/m² on Day 1 of the first cycle and 500 mg/m² on Day 1 of Cycles 2 to 6. - On days when bendamustine and rituximab are to be administered, rituximab will be administered prior to bendamustine. - Rituximab administration by IV push or bolus or subcutaneous administration is prohibited. - Rituximab should be administered according to local institutional standards with appropriate premedications. Refer to the local prescribing information for rituximab (or for the approved biosimilar that is being used) for detailed administration and safety instructions (US prescribing information is provided for reference: Rituximab USPI; Rituximab biosimilars: Riabni™ USPI; Ruxience™ USPI; Truxima® USPI).

6.2. Preparation/Handling/Storage/Accountability

6.2.1. Arm A Preparation/Handling/Storage: Pirtobrutinib

Pirtobrutinib tablets are available at strengths of 25 mg, 50 mg, and 100 mg and will be provided to the sites in bottles. The site pharmacist will dispense bottles to the patient in an amount necessary to allow for outpatient administration. Tablets are to be stored at room temperature.

6.2.2. Arm B Preparation/Handling/Storage: Bendamustine plus Rituximab (BR)

Preparation, storage and handling for bendamustine and rituximab, will be according to instructions provided in the local label for the individual product.

6.3. Measures to Minimize Bias: Randomization

This is an open-label study. Randomization will be used to minimize bias in the assignment of patients to treatment groups, to increase the likelihood that known and unknown patient attributes (e.g., demographic and baseline characteristics) are evenly balanced, and to enhance the validity of statistical comparisons across treatment groups.

This study will use an interactive voice/web response system (IWRS) for randomization. All patients will be centrally assigned to randomized study treatment using IWRS. Patients will be randomized 1:1 between Arm A:Arm B, and will be stratified based on IGHV mutation status (mutated versus unmutated), and on Rai stage (low/intermediate versus high).

If a patient withdraws from the study, then his/her enrollment/randomization code cannot be reused. Withdrawn patients will not be replaced.

6.4. Study Intervention Compliance

For patients randomly assigned to pirtobrutinib, compliance with study treatment will be assessed at each visit. Compliance will be assessed by direct questioning, counting returned tablets, and reviewing patient diaries. Deviation(s) from the prescribed dosage regimen should be recorded in the electronic case report form (eCRF).

A patient will be considered noncompliant if he or she takes < 75% of the planned doses for assigned study drug in a cycle. A patient will also be considered noncompliant if he or she is judged by the Investigator to have intentionally or repeatedly taken $\geq$ 125% of the planned doses of study drug over the course of the patient's treatment.

Study treatment that is administered IV will be administered only at the investigational sites by the authorized study site personnel. As a result, treatment compliance is ensured.

6.5. Concomitant Therapy

Concomitant medications will include ongoing medications and all medications that were administered within 14 days prior to the planned start of study drug (i.e., from Screening) through the Safety Follow-up (SFU) visit (at least 28 days [+7 days] after the last dose of study treatment) and are to be recorded in the eCRF. Information regarding reason for use and dates of administration including start and end dates should be recorded in eCRF. These concomitant medications are to include prescription and nonprescription medications, transfusions, growth factor support, vitamins, nutritional supplements, herbal supplements and other remedies. Excluded medications for eligibility are indicated in the Exclusion Criteria (Section 5.2).

6.5.1. Allowed Concomitant Medication and Supportive Care

- Oral contraceptives, hormone-replacement therapy, or other maintenance therapy (denosumab, bisphosphonates, and other medications for the treatment of osteoporosis) should be continued for the duration of the study.
- Standard supportive medications may be used in accordance with institutional guidelines and Investigator discretion. These may include:
 - Hematopoietic growth factors to treat neutropenia, anemia, or thrombocytopenia in accordance with American Society for Clinical Oncology guidelines;
 - Red blood cells (RBCs) and platelet transfusions;
 - Anti-emetic,
 - Analgesic, and
 - Antidiarrheal medications;
 - Electrolyte repletion (e.g., calcium and magnesium) to correct low electrolyte levels;
- Glucocorticoids (≤ 20 mg per day prednisone or equivalent) are allowed preferably for a duration of ~ 14 days or less, unless there is a compelling clinical rationale for a higher dose or longer duration articulated by the Investigator and approved by the Sponsor). Anticipated uses may be short courses to treat asthma or chronic obstructive pulmonary disease (COPD).
- Standard of care medications, including hormonal therapy for patients with prostate cancer (e.g., gonadotropin-releasing hormone [GnRH] or luteinizing hormone-releasing hormone [LHRH] agonists) and breast cancer (e.g., GnRH/LHRH agonists, aromatase inhibitors, selective estrogen receptor modulators [SERMs] or degraders [SERDs]), that the patient has been receiving for at least 28 days prior to enrollment, are allowed if the disease for which the therapy is provided is not a study exclusion or provided they are not on the list of prohibited concomitant medications (refer to Section 6.5.1.1).
- Local treatment while receiving study treatment (e.g., palliative radiation therapy for symptomatic nodal disease) is permitted if the patient is not considered to be clinically or radiographically progressing. If the lesion that is to be treated is a target lesion, the lesion will be censored at the time of treatment. However, the patient may remain on study provided there is other evidence of disease that can be followed for determination of progression. If the patient will receive local treatment for symptomatic progression, continuation of therapy post progression is allowed as outlined in Section 6.7.
- Prophylactic antibiotic or IV immunoglobulin (IVIG) therapy for management of patients at risk of infections is recommended. Provide prophylaxis treatment for *Pneumocystis jirovecii* pneumonia (PCP) and herpes virus infections for patients during treatment with rituximab and for up to 12 months following treatment as appropriate. Local practices or guidelines regarding infection prophylaxis must be followed.
- The Sponsor recommends holding pirtobrutinib and bendamustine for at least 3 days before and after surgery where bleeding risk cannot be excluded. Any concern for disease flare due to a prolonged pirtobrutinib dose interruption should be discussed with the Sponsor, who may permit holding pirtobrutinib for a shorter period of time.

- Premedications should include a minimum of acetaminophen and an antihistamine before each infusion of rituximab based on institutional guidelines and according to local prescribing information.

6.5.1.1. COVID-19 Vaccination and Response Assessment

- COVID prophylaxis and treatment are allowed. As with any acute patient safety event, the use of potentially lifesaving therapy is permitted. This applies to all available oral and intravenous antiviral therapy, as well as to antibody and immunosuppressive treatments that are part of the management of patients diagnosed with COVID-19 or of those who are candidates for prophylactic treatment. These interventions should not be received via enrollment to an additional clinical trial unless access is otherwise unavailable. In those instances, the Sponsor should be contacted for approval. Please refer to [Section 10.5](#) [Appendix 5](#) of the protocol, pirtobrutinib investigator brochure, and comparator drug package insert for potential drug-drug interactions.
- The Sponsor recommends that when medically appropriate and feasible, patients receive primary and/or booster SARS-CoV-2 vaccine doses prior to initiating treatment. However, patient autonomy and clinical judgment may also guide these decisions. Should the patient receive the vaccine(s) during the study period, please follow eCRF instructions for concomitant medication recording.
- COVID-19 vaccination has been shown to cause transient, reactive adenopathy in approximately 10% of patients. Typically enlarged axillary, cervical, and supraclavicular lymph nodes in the vicinity of the drainage area of the injection site have been observed transiently ([Herishanu et al. 2021](#); [Lehman et al. 2021](#); [Tu et al. 2021](#)). Such transient enlargement of lymph nodes may resemble PD and therefore may confound the interpretation of response assessment. Although response assessment should be performed according to the SoAs ([Section 1.3](#)), the following recommendations should be considered for potential COVID-19 vaccination patients:
 - If a COVID-19 vaccine is scheduled around the same time as an imaging visit for this study, it is preferable that if scheduling permits, the scans should be done before the COVID-19 vaccination.
 - If a vaccination has already occurred near the imaging visit, the imaging schedule should continue to be followed, without delaying patient care.

If adenopathy is observed in the vicinity of the drainage area of the COVID-19 vaccination injection site and is the only evidence of possible PD, a follow-up scan after 6 to 8 weeks should be considered as this adenopathy should be transient and should resolve in this time period.

6.5.2. Restricted Concomitant Medication

- Pirtobrutinib inhibits P-gp and is a moderate inhibitor of CYP2C8 and BCRP in the clinic. Concomitant use of pirtobrutinib with sensitive P-gp, CYP2C8, or BCRP substrates increases their plasma concentrations, which may increase the risk of adverse reactions related to these substrates. Recommendations for sensitive P-gp, CYP2C8, or BCRP substrates provided in

their approved product labeling should be followed (refer to Section 10.5, Appendix 5 for a list of sensitive P-gp and CYP2C8 substrates).

- The coadministration of bendamustine with CYP1A2 inhibitors may increase bendamustine plasma concentrations and may result in an increased incidence of adverse reactions. Consider alternative therapies that are not CYP1A2 inhibitors during treatment with bendamustine. The coadministration of bendamustine with CYP1A2 inducers may decrease bendamustine plasma concentrations and may result in decreased efficacy. Consider alternative therapies that are not CYP1A2 inducers during treatment with bendamustine. Please refer to local labels for bendamustine (US prescribing information provided for reference: [Bendamustine USPI](#)).
- Except as indicated in Section 6.5.1, patients are not allowed to receive concomitant systemic anti-cancer agents, hematopoietic growth factors for prophylaxis in Cycle 1, therapeutic monoclonal antibodies, drugs with immunosuppressant properties, or any other investigational agents. No new or alternative systemic anticancer therapy is allowed prior to documentation of PD in accordance with protocol specified disease response criteria.
- Live-virus vaccines should not be given at any time during study treatment, including prior to and while receiving rituximab treatment, or during trial participation unless B-cell levels have returned to normal.
- Therapeutic anticoagulation with warfarin or another Vitamin K antagonist is not allowed.

6.5.3. Subsequent Anticancer Therapy

Administration of subsequent anticancer therapy for CLL/SLL is not allowed until:

- PD is established according to the iwCLL 2018 criteria.
- Withdrawal from study treatment as described in Section 7.

After study drug treatment is complete, the following information on subsequent anticancer therapies will be collected approximately every 16 weeks from the end of safety follow up for the first 2 years after discontinuation from study treatment and approximately every 24 weeks thereafter until death, withdrawal by patient, lost to follow-up, or study terminated by Sponsor, whichever comes first:

- Receipt of all subsequent anticancer therapies.
- iwCLL 2018 criteria indication for initiation of subsequent anticancer therapy.
- Response to all subsequent anticancer therapies.

6.6. Dose Modification Guidelines

Dose modifications are allowed for management of study treatment related toxicities. If dose modification of study treatment is required for any AE not related to study treatment, the planned dose modification should be reviewed with the Sponsor. Toxicity must resolve to Grade ≤ 1 or baseline prior to resuming the next cycle except AEs with no immediate medical consequence

that can be controlled with adequate treatment (e.g., pain, alopecia, neuropathy, fatigue, nausea, vomiting, diarrhea, Grade 2 hypothyroidism, or Grade 2 hypertension).

Any overdose or incorrect administration of pirtobrutinib, bendamustine, or rituximab should be noted on the Study Drug Administration eCRF. AEs associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF.

Regardless of treatment arms, for dose delays, the cycle schedule will be shifted accordingly (refer to instructions for data entry in the eCRF guidelines). The protocol schedule of radiographic imaging CT/ magnetic resonance imaging (MRI) scans will remain fixed, however.

For patients in Arm A: Pirtobrutinib may be held for up to 28 days from the last dose to allow time to recover from toxicity. In exceptional circumstances, a longer delay may be permitted upon agreement between the Investigator and the Sponsor.

For patients in Arm B: Initiation of a dose of bendamustine, or rituximab may be delayed for a maximum of 28 days to allow a patient sufficient time for recovery from study treatment-related toxicity. In exceptional circumstances, a longer delay may be permitted upon agreement between the Investigator and the Sponsor.

All dose interruptions and dose modifications and the reasons for those changes will be recorded in the eCRF.

Dose reductions should be made according to the instructions outlined in Sections 6.6.1 and 6.6.2.

6.6.1. Dose Modifications and Toxicity Management Guidelines for Arm A: Pirtobrutinib

Dose hold and/or reduction will be implemented for any patient who experiences a clinically significant hematologic AE (i.e., $\geq$ Grade 3, or > 1 grade change from baseline if baseline is Grade 2 or above) as assessed by the National Cancer Institute Common Terminology Criteria in Adverse Events v5.0 (NCI CTCAE v5.0).

For each patient, a maximum of 2 dose reductions will be allowed, unless there is a compelling clinical rationale for additional dose reduction(s) articulated by the Investigator and approved by the Sponsor.

Table 6.3 Dose Modifications for Pirtobrutinib

Adverse Events ^a	Occurrences Requiring Dose Modification	Pirtobrutinib (Starting dose 200 mg QD)	ARM A (pirtobrutinib) Modification
• Grade 3 or greater non-hematologic toxicity^b, • Grade 3 neutropenia with fever and/or infection^c, • Grade 4 neutropenia lasting ≥ 7 days, • Grade 3 thrombocytopenia with bleeding, or • Grade 4 thrombocytopenia	First occurrence	No change	Hold pirtobrutinib until recovery to Grade 1 or baseline; may restart at original dose level (200 mg QD)
	Second occurrence	100 mg QD	Hold pirtobrutinib until recovery to Grade 1 or baseline; may restart at one dose level lower (100 mg QD)
	Third occurrence	50 mg QD	Hold pirtobrutinib until recovery to Grade 1 or baseline; may restart at one dose level lower (50 mg QD)
	Fourth occurrence	Discontinue	Discontinue

a Dose modification is not recommended for asymptomatic lymphocytosis or asymptomatic lipase increase .

b Please refer to Section 8.4.5.10 for additional dose modification guidelines for hepatic events .

c Consider supportive measures, including antimicrobials and growth factors (e.g., G-CSF), as per ASCO guidelines or institutional standards.

If pirtobrutinib dose is reduced for apparent treatment-related toxicity, the dose need not be re-escalated, even if there is minimal or no toxicity with the reduced dose. However, if the patient tolerates a reduced dose of pirtobrutinib for ≥ 2 weeks then the dose may be re-escalated to the next higher dose level, at the discretion of the Investigator and with written approval of the Sponsor. Repeat re-escalation, not to exceed the starting dose, may be considered if tolerated as outlined. Such re-escalation may be warranted if AE that led to the dose reduction was not treatment-related.

In the event of dosing delays or holds due to toxicity, and subsequent restarting of study drugs, the cycle schedule will be shifted accordingly (refer to instructions for data entry in the eCRF guidelines). The protocol schedule of radiographic imaging CT/MRI scans will remain fixed, however.

6.6.2. Dose Modifications and Toxicity Management Guidelines for Arm B: Bendamustine plus Rituximab

6.6.2.1. Dose Modifications for Bendamustine

Please refer to the bendamustine local label for the current dose modification and toxicity management guidelines for bendamustine. The following information provides a summary of dose modification from the USPI for bendamustine. The conventional criteria for toxicity may be difficult to evaluate and require careful consideration of the underlying disease.

Dose modifications for hematologic toxicity in patients with CLL/SLL should be made with the consideration of an increased frequency of abnormal hematologic parameters at baseline.

If the patient has disease-related splenomegaly or significant bone marrow involvement resulting in cytopenia determined to be non-clinically significant, treatment may continue at the Investigator's discretion without dose modification.

Additional guidance for dose modification of bendamustine is available in the package insert (refer to the local label). Bendamustine administration should be delayed in the event of Grade 4 hematologic toxicity or clinically significant Grade ≥ 2 nonhematologic toxicity. Once nonhematologic toxicity has recovered to Grade ≤ 1 and/or the blood counts have improved ($ANC \geq 1 \times 10^9/L$, platelets $\geq 75 \times 10^9/L$), bendamustine can be reinitiated at the discretion of the treating physician. In addition, dose reduction may be warranted (refer to Warnings and Precautions for Myelosuppression in the local label for bendamustine).

Bendamustine should be used with caution in patients with mild hepatic impairment. Bendamustine should not be used in patients with moderate (AST or ALT $2.5\text{--}10\times$ ULN and total bilirubin $1.5\text{--}3\times$ ULN) or severe (total bilirubin $> 3\times$ ULN) hepatic impairment.

Bendamustine should be used with caution in patients with mild or moderate renal impairment and should not be used in patients with $CrCl < 40$ mL/min. If bendamustine is discontinued, patients can continue to receive rituximab up to the maximum number of infusions allowed on this protocol.

Table 6.4 Dose Modifications for Bendamustine

Grade ≥ 3 Hematologic Toxicity	
First Occurrence	Reduce the dose to 50 mg/m ² IV on Days 1 and 2 of each cycle
Second Occurrence	Reduce the dose to 25 mg/m ² IV on Days 1 and 2 of each cycle
Grade ≥ 3 Nonhematologic Toxicity	
First Occurrence	Reduce the dose to 50 mg/m ² IV on Days 1 and 2 of each cycle

In the event of dosing delays due to toxicity, study treatment dosing of both bendamustine and rituximab should be held, and re-administered together once toxicity has resolved to Grade 1 or better (or to study baseline).

In the event of dosing delays or holds due to toxicity, and subsequent restarting of study drugs, the cycle schedule will be shifted accordingly (refer to instructions for data entry in the eCRF guidelines). The protocol schedule of radiographic imaging CT/MRI scans will remain fixed, however.

Patients should be asked about symptoms suggestive of infusion related reactions after their first cycle of therapy. Monitor clinically and discontinue drug for severe reactions.

Patients who experienced Grade 3 or worse allergic-type reactions were not typically rechallenged. Measures to prevent severe reactions, including antihistamines, antipyretics and

corticosteroids should be considered in subsequent cycles in patients who have previously experienced Grade 1 or 2 infusion reactions. Discontinuation should be considered in patients with Grade 3 or 4 infusion reactions.

Study drug treatment (both bendamustine and rituximab) may be held a maximum of 28 consecutive days for a clinically significant toxicity. Study treatment should be discontinued in the event of a toxicity lasting > 28 days, unless reviewed and approved by the Sponsor.

If bendamustine is discontinued, patients can continue to receive rituximab up to the maximum number of infusions allowed on this protocol.

6.6.2.2. Dose Modifications for Rituximab

No dose modification is allowed for rituximab. Patients at high risk for infusion reactions with rituximab may, at the Investigator's discretion, receive the initial dose of rituximab split over 2 consecutive days (C1D1 and Cycle 1 Day 2 [C1D2]). Refer to the rituximab local label (or label for the approved biosimilar that is being used) for administration of rituximab. Rituximab should be administered according to local institutional standards with appropriate premedications.

If rituximab is discontinued, patients can continue to receive bendamustine as outlined in this protocol.

If bendamustine is discontinued, patients can continue to receive rituximab up to the maximum number of infusions allowed on this protocol.

6.7. Intervention after the End of the Study

The end of the study is defined in Section 4.4. Investigators will continue to follow the SoAs provided in Section 1.3 until notified by the Sponsor that the end of the study has occurred.

6.7.1. Treatment after Progression / Study Completion

Patients considered for treatment beyond progression must not have symptomatic progression (examples include patients with progression based on lymphocytosis in the absence of evidence of bone marrow failure, or patients with isolated asymptomatic nodal progression).

For patients randomized to Arm A: It is anticipated that a patient on this study will receive study treatment with pirtobrutinib until the patient is able to obtain commercially available pirtobrutinib in their respective country, if the patient does not meet criteria requiring discontinuation of treatment, and the patient's participation in the study has not ended. Upon commercial availability in each patient's respective country, there may be additional options for the patient to continue to receive pirtobrutinib once the regulatory requirements are satisfied. These may include, but are not limited to a rollover trial, patient assistance (should the patient qualify), or commercial pirtobrutinib. The study may be terminated if pirtobrutinib does

not obtain marketing approval or the development of pirtobrutinib is no longer being pursued by the Sponsor.

For patients receiving Arm B: As study drugs used in Arm B are all locally approved and marketed, the patients on this study treatment may continue treatment as commercially available therapy via physician prescription.

The Sponsor reserves the right to discontinue the study for clinical or administrative reasons at any time.

6.7.2. Crossover to Pirtobrutinib

The SoA for optional crossover treatment (for patients crossing over from Arm B to Arm A) is provided in Section 1.3.3.

6.7.2.1. Rationale for Crossover

Due to the promising benefit/risk profile of pirtobrutinib in Arm A, and the safety profile observed to date, patients who are randomized to Arm B may be eligible for crossover to provide access to pirtobrutinib while on study, and will continue to be monitored for safety and efficacy. Additionally, allowing crossover will provide the opportunity for patients who either completed the assigned treatment or discontinued treatment due to toxicity to continue to be followed per protocol.

6.7.2.2. Patients who Cross Over upon IRC-confirmed PD

The EOT assessment should be completed within 7 days of last dose (date of last dose must be recorded in EDC) or decision to terminate initial treatment (when patient is assigned to treatment and decision to end treatment is made before first dose is taken, record the date of end of treatment decision in EDC) as indicated in SoA (Section 1.3.3). The SFU assessment is required after EOT. However, CO-C1D1 pre-dose assessment can replace SFU if it occurs within 28 days of the last dose of Arm B treatment.

6.7.2.3. Patients who Discontinue Treatment in Arm B for Reasons other than PD

Patients who discontinue treatment in Arm B for reasons other than PD, but may potentially crossover upon IRC-confirmed PD at a later time point:

- The EOT assessment should be completed within 7 days of last dose (date of last dose must be recorded) or decision to terminate initial treatment (when patient is assigned to treatment and decision to end treatment is made before first dose is taken, record the date of end of treatment decision) as indicated in SoA (Section 1.3.3).
- The SFU assessment should follow the EOT assessment.
- LTFU assessment and procedures will be conducted in accordance with SoAs in Section 1.3.1 or 1.3.2.

- Crossover Screening assessments should be conducted within 42 days of IRC-confirmed PD.

6.7.3. End of Treatment

Patients who discontinue treatment for reasons other than PD should remain on study and continue to have disease assessments performed per protocol as part of LTFU (refer to Section 6.7.5; patients who cross over are discussed in Section 6.7.2). For all study treatments, the End of Treatment (EOT) assessments and procedures will be conducted in accordance with the SoAs (Section 1.3).

Patients receiving BR who discontinue from the study treatment for reasons other than PD and before completion of the planned 6 cycles of therapy should remain on study and continue to have disease assessments performed per protocol as follow up for progression and survival. For all patients treated with BR, whether discontinuing prematurely or at the completion of 6 cycles of therapy, an EOT assessment should occur within 7 days of last dose of study treatment or decision to terminate study treatment. Patients will have a separate SFU visit to determine the status of any unresolved AEs (Section 6.7.4).

6.7.4. Safety Follow-up

The SFU assessments will be conducted 28 days (+7 days) after the last dose in accordance with the SoAs (Section 1.3). Safety follow-up procedures may be performed as part of the EOT visit if the latter was performed ≥ 28 days (+7 days) after the final dose of the last cycle (e.g., for patients who discontinue therapy after an extended study drug hold).

6.7.5. Long-Term Follow-up

The LTFU assessments and procedures will be conducted in accordance with the SoAs (Section 1.3). LTFU assessments will occur every 16 weeks (± 4 weeks) for 2 years relative to C1D1 and every 24 weeks (± 4 weeks) thereafter, until the patient withdraws consent for further participation, is lost to follow-up, has died, or close of the study. If a patient discontinues study treatment for reasons other than PD, death, lost to follow-up, or withdrawal of consent, the patient will be followed for disease assessment at regular intervals until PD as specified in Section 10.7, Appendix 7) utilizing the same modality(ies) used for the baseline imaging assessment. In addition to monitoring for progression, assessments may include subsequent anticancer therapy(ies) and survival status. Investigators should follow up and report the occurrence of the second primary malignancy for up to 5 years since the start of the study medication (Refer to Section 8.6).

LTFU may be conducted by phone when response assessment is not scheduled. Unscheduled interactions which may also constitute a LTFU assessment can be reported in the appropriate eCRF.

For any patient who is lost to follow-up, the study site will attempt to ascertain survival information via public database search. If survival status still cannot be ascertained, patients will be considered lost to follow-up and will be censored appropriately.

7. DISCONTINUATION OF STUDY INTERVENTION AND PATIENT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

Patients will be advised that they are free to discontinue study treatment at any time and that they will be followed for survival after discontinuing treatment (refer to Section 6.7.4). Over the course of the study, the Investigator and/or the Sponsor should discontinue a patient from treatment for any of the reasons listed below:

- PD per iwCLL 2018 criteria

Exception: Patients with documented PD who are tolerating treatment on Arm A and, in the opinion of the Investigator, are deriving clinical benefit from continuing study treatment, may continue treatment with prior Sponsor approval.

Patients considered for treatment beyond progression must not have symptomatic progression (examples include patients with progression based on lymphocytosis in the absence of evidence of bone marrow failure, or patients with isolated asymptomatic nodal progression).

- Unacceptable toxicity
- Intercurrent illness compromising ability to fulfill protocol requirements
- The patient becomes pregnant during the study
- Requirement for alternative treatment in the opinion of the Investigator, unless such treatment is temporary (e.g., local radiation or surgery needed to palliate symptoms of the disease that does not otherwise meet the definition of PD)
- If receiving pirtobrutinib, dose delay > 28 days for hematologic toxicity, unless a clinical need for prolonged delay has been determined by the Investigator with documented Sponsor approval. For Arm B patients with dose delay > 28 days for unacceptable toxicity, consult product package insert.
- Patient is noncompliant, with study procedures and/or treatment upon review with the Sponsor
- Any medical condition that the Investigator determines to be a clinically significant finding which is identified after enrollment and which may jeopardize the patient's safety if study treatment is continued.
- Withdrawal of consent
- Investigator decides that the patient should be discontinued from study treatment.
- Lost to follow-up
- Death
- Study terminated by Sponsor

At the time a patient discontinues treatment, all safety data normally required at the EOT visit will be obtained if possible, as outlined in Section 6.7.3. Patients will enter LTFU where they may be required to undergo disease assessments (refer to Section 6.7.4). Patients who discontinue on Arm B may be considered for crossover to Arm A as determined by eligibility (refer to Section 5.3).

7.2. Patient Discontinuation/Withdrawal from the Study

Patients will be discontinued under the following circumstances

- Participation in the study needs to be stopped for medical, safety, regulatory, compliance or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP)
- Death
- Patient is lost to follow up
- Patient or patient's designee withdraws consent
- Study terminated by the Sponsor

If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent. If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

7.2.1. Discontinuation of Inadvertently Enrolled Patients

If the Sponsor or Investigator identify a patient who did not meet enrollment criteria and was inadvertently enrolled, the Sponsor and Investigator will determine if it is medically appropriate to continue. The Investigator must obtain documented approval from the Sponsor to allow the inadvertently enrolled patient to continue in the study.

Patients will adhere to the protocol specified assessments including SFU which is as outlined in the SoAs (Section 1.3), Section 8.6 (Adverse Events and Serious Adverse Events), and Section 8.4 (Safety Assessments).

7.3. Lost to Follow-up

A patient will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. Site personnel are expected to make diligent attempts to contact patients who fail to return for a scheduled visit or were otherwise unable to be followed up by the site.

Discontinuation of specific sites or of the study as a whole is described in Section 10.1.11.2.

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoAs. Protocol waivers or exemptions are not allowed. Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the patient should continue or discontinue study treatment. Adherence to the study design requirements, including those specified in the SoAs, is essential and required for study conduct.

8.1. Screening

All Screening evaluations must be completed and reviewed by the appropriate site personnel to confirm that potential patients meet all eligibility criteria.

The Investigator will maintain a Screening log to record details of all patients screened and to confirm eligibility or record reasons for Screening failure, as applicable.

Procedures conducted as part of the patient's routine clinical management (e.g., blood counts, scans) and obtained before signing of the ICF may be utilized for Screening or baseline purposes, provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoAs (Section 1.3).

Screening results within 3 days of C1D1 are acceptable as C1D1 results.

8.2. Medical History

Patient complete medical history should include disease related signs and symptoms, initial date of CLL/SLL diagnosis, and Rai stage.

Any disease related complications including immune mediated complications (immune mediated thrombocytopenia or hemolysis) should be recorded if data is available.

8.3. Efficacy Assessments

8.3.1. Response Assessments

Response will be assessed by the Investigator and the IRC based on physical examination, imaging, hematology results and bone marrow examinations as described using the iwCLL 2018 response criteria which will include partial remission with lymphocytosis (PR-L), complete remission with an incomplete marrow recovery (CRi) and nodular partial remission (nPR) (Hallek et al. 2018, Cheson et al. 2012; Section 10.7, Appendix 7). A central radiology vendor will be used to collect images for IRC review. All patients must have clinical examination and response assessments during the course of treatment, while on study, and during follow up as indicated in the SoAs (Section 1.3).

With approved BTK inhibitors, lymphocytosis and leukocytosis are well-documented on--target effects that occur early during administration of study treatment. These reactions are not

reflective of PD in the absence of other signs of PD (e.g., splenomegaly, enlarging lymph nodes, disease-related constitutional symptoms) will not be considered PD. Guidance for recording of disease-related symptoms is provided in Section 8.4.3.

All measurable disease must be documented at Screening and reassessed at scheduled timepoints indicated in the SoAs (Section 1.3).

Radiologic disease assessment will be conducted by the Investigator in accordance with the SoAs (Section 1.3) and the Imaging Manual. Investigators should use the same method consistently for an individual patient throughout the study. Both CLL and SLL responses will be assessed per iwCLL 2018 criteria (Section 10.7, Appendix 7). CT scan with IV contrast agent is the preferred method of assessment with scans of neck, chest, abdomen and pelvis. However, MRI is acceptable if CT scan with contrast agent is contraindicated.

For patients with documented disease involving blood/bone marrow, but with no documented baseline radiographic findings and thus where radiology is not required for routine response assessment, imaging is to be performed every 24 weeks according to the SoAs (Section 1.3).

If patient terminates treatment prior to a scheduled response assessment, the patient should have that response assessment done at the EOT visit. This assessment does not need to be repeated if performed within 2 weeks prior to the EOT visit, or if tumor progression was previously determined.

A bone marrow aspirate and biopsy, to include karyotype, should be collected during Screening and for confirmation of CR per the SoAs (Section 1.3), and submitted for central assessment. Refer to Section 8.10. Guidance on sample collection and timing is provided in the Laboratory Manual.

According to iwCLL 2018 criteria, diagnosis of Richter's transformation is established by biopsy of the affected site (not required for this study). However, if per local standard of care or at Investigator discretion, an ancillary whole PET-CT scan (not required for study) is performed, the results of this scan should be captured in the EDC as directed in the CRF Completion Guidelines.

8.3.2. IRC Assessments

Response assessments will be assessed by the IRC. Disease assessment (including scans and other disease assessments) will continue until IRC confirmed PD. These data will constitute the primary assessment for PFS analysis, following IRC review. All scans, regardless of patient treatment status should be sent for IRC review, except scans from patients in crossover arm. Prior to crossover from Arm B to Arm A (Section 6.7.2), a patient may continue treatment and remain under close observation until progression is confirmed by the IRC.

8.4. Safety Assessments

8.4.1. Vital Signs

Vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature) will be assessed after the patient has rested in the sitting position.

8.4.2. Physical Examination

The Screening physical examination will include, at a minimum, the general appearance of the patient, height (Screening only) and weight, and examination of the skin, eyes, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal system, nervous system, and lymphatic system.

Symptom-directed physical exams will be done during the treatment period, at the EOT and SFU visits, and during the post-treatment disease follow-up.

8.4.3. Disease-related Symptoms

Will be assessed and recorded in the patient records and are defined per [Hallek 2018](#) as:

- a) Unintentional weight loss of 10% or more within the previous 6 months;
- b) Significant fatigue (i.e., ECOG PS 2 or worse; inability to work or perform usual activities);
- c) Fevers higher than 100.5°F or 38°C for 2 or more weeks without other evidence of infection; or
- d) Night sweats for more than 1 month without evidence of infection

8.4.4. Electrocardiograms

Electrocardiogram (ECG) monitoring should be performed in accordance with the SoA for the treatment arm (Arm A SoA in Section 1.3.1; Arm B SoA in Section 1.3.2; Crossover SoA in Section 1.3.3). To minimize variability, it is important that patients are in a resting position for at least 5 minutes prior to ECG evaluation. Body position should be consistently maintained for each ECG to prevent changes in heart rate. ECGs for each patient should be obtained from the same machine whenever possible. Any clinically significant changes in ECGs that occur during the study should be reported as an AE in the eCRF which will also collect pertinent clinical information.

Loxo may request de-identified copies of the ECGs for adjudication. Sites are required to submit ECG tracings for Sponsor review in these circumstances.

- Manually review ECGs to confirm accuracy. ECGs must be interpreted by a qualified physician (the Investigator or qualified designee) at the site for immediate patient management.

- If the ECG is abnormal,
 - Assess for all possible causes (concomitant medications, electrolyte abnormalities, underlying cardiac conditions, etc.).
 - Clinical chemistry should be assessed and if electrolytes are abnormal, they should be repeated as indicated. Potassium should be ≥ 4 meq/L and less than ULN and magnesium and calcium should be within normal limits.
 - Serial repeat ECG collection to ensure resolution should be conducted as clinically appropriate.
- If patients have an underlying BBB, ECGs must be manually reviewed by a qualified physician and the QTc value must be corrected (utilizing locally approved correction factors or based upon guidance provided in Section 10.8, Appendix 8) and this value should be entered into the eCRF.
- If an unscheduled ECG is done at any time, then an electrolyte panel (i.e., calcium, magnesium, and potassium) must be done to coincide with the ECG testing.
- If triplicate ECGs are obtained to confirm a Grade 3 AE (QTcF ≥ 501 msec) as outlined in the NCI CTCAE v5.0 criteria, ECGs should be collected approximately 1 minute apart, and the cumulative collection time for all three ECGs should not exceed 5 minutes.
- Patients should be clinically monitored for symptoms of cardiac arrhythmias (e.g., palpitations, lightheadedness, syncope, chest pain) or new onset dyspnea. ECG should be done as clinically indicated for assessment with electrolyte panel. If a clinically significant arrhythmia is discovered (e.g., atrial fibrillation/atrial flutter), the clinical circumstances surrounding the time of onset (if known; e.g., time/date of onset, activity and/or lifestyle changes/factors at the time of onset, associated symptoms, laboratory values) must be documented in the eCRF and study required documents and provided as requested by the Sponsor.

8.4.5. Clinical Safety Laboratory Assessments

All protocol-required laboratory assessments must be conducted in accordance with the Laboratory Manual and the SoAs (Section 1.3). Sites with documentation specifying certain analytes or procedures are not collected per site policy or local regulation will not be considered protocol deviations if Sponsor approval is granted.

Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the patient's condition. Clinically significant laboratory results should be reported as AEs (AE section of the eCRF) if the results require a change of study treatment or require medical intervention.

- The Investigator must review the laboratory report, document this review, and record any clinically significant abnormalities occurring during the study.
- The laboratory reports must be filed with the source documents.

- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 7 days after the last dose of study treatment should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator.
 - If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, additional etiologies should be identified and reported as an AE as appropriate.
 - If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in patient management or are considered clinically significant by the Investigator especially if resulting in study treatment management (e.g., dose modification), reporting of the abnormality (e.g., AE or SAE) should be performed and recorded in the eCRF.

Local laboratories will be utilized for routine laboratory tests and SFU (e.g., blood chemistries from serum or plasma, hematology, and urinalysis). Special assessments will be performed centrally, including hematology tests associated with IRC assessment of response and PK studies. Additional guidance regarding testing and handling and processing of samples for central assessment is provided in the Laboratory Manual.

8.4.5.1. Hematology

Hematology should be assessed locally in accordance with the SoAs (Section 1.3). In addition, at each response assessment, a sample is required to be submitted centrally, as a component of the IRC assessment of disease response. Patients on crossover will be assessed locally by the Investigator. Hematology assessments will include: hemoglobin, hematocrit, RBC count, white blood cell (WBC) count, platelet count, percent or absolute differential (neutrophils, lymphocytes, eosinophils, and monocytes).

8.4.5.2. Blood Chemistry

Blood chemistry from serum or plasma should be assessed locally in accordance with the SoAs (Section 1.3) and should include assessment of the following: sodium, potassium, chloride, glucose, creatinine, total protein, albumin, total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST). Alkaline phosphatase can be performed as needed. Direct (or indirect) bilirubin should be performed at any time total bilirubin is abnormal. As indicated in the SoA, LDH, calcium, magnesium, phosphorus and uric acid are required at Screening and C1 of each Cycle 1-6.

If an unscheduled ECG is done at any time, then an electrolyte panel (i.e., calcium, magnesium, and potassium) should be done to coincide with the ECG testing if clinically feasible (this is also noted in ECG instructions on each SoA in Section 1.3).

8.4.5.3. Beta-2 microglobulin

Beta-2 (B2) microglobulin test should be assessed locally in accordance with the SoAs (Section 1.3).

8.4.5.4. Serum immunoglobulins

Local assessment of serum immunoglobulins should include IgG, IgM, and IgA levels.

8.4.5.5. CMV Testing

Local CMV testing at Screening must include serologic testing for CMV IgG, IgM, and DNA PCR testing.

8.4.5.6. Coagulation

The coagulation panel should include activated partial thromboplastin time (aPTT) and prothrombin time (PT) or international normalized ratio (INR) and should be assessed locally.

8.4.5.7. Urinalysis

Urinalysis that includes color, specific gravity, pH, glucose, bilirubin, occult blood, protein, leukocytes, and urobilinogen should be assessed locally in accordance with the SoAs (Section 1.3).

8.4.5.8. Pregnancy Testing

For women of child bearing potential (WOCBP): Pregnancy testing (serum or urine) must be conducted in accordance with the SoAs (Section 1.3) or as required per local regulations and/or institutional guidelines and may be performed locally. Pregnancy reporting guidance is provided in Section 8.6.5. WOCBP are defined as women who are following menarche, and who are not postmenopausal (or 2 years of non-therapy-induced amenorrhea) or surgically sterile. For patients in both arms, pregnancy tests must be performed at screening, within 24 hours before C1D1, monthly during treatment, and at EOT and SFU visits. Patients enrolled in Arm B will continue with monthly pregnancy testing for 12 months from the last dose of rituximab. If any urine pregnancy test is positive, study treatment will be delayed until the patient pregnancy status is confirmed by a serum pregnancy test. If serum pregnancy test is positive, the patient will be permanently discontinued from study treatment.

8.4.5.9. Viral Testing

Hepatitis testing should be assessed at Screening in accordance with the SoA (Section 1.3) and should include testing for hepatitis B (hepatitis B surface antigen [HBsAg], hepatitis B surface antibody [HBsAb], and total hepatitis B core antibody [HBcAb]) and hepatitis C virus (HCV) antibody serology. Screening for CMV includes IgM, IgG and CMV DNA by PCR. If other testing indicates acute or chronic infection or reactivation of infection, obtain viral load (e.g.,

quantitative hepatitis B virus [HBV]-DNA, HCV-RNA). Patients with evidence of active hepatitis B and/or hepatitis C infection (as defined in the exclusion criteria) are excluded from participation in the trial.

Patients with known active CMV infection and/or a history of positive HIV test (regardless of CD4 count) are excluded from participation in the trial due to potential drug-drug interactions between anti-retroviral medications and pirtobrutinib and risk of opportunistic infections with both HIV and approved BTK inhibitors.

8.4.5.10. Hepatic Safety Monitoring

Hepatic laboratory studies should be assessed locally in accordance with the SoA (Section 1.3). Reference hepatic laboratory parameters that may be necessary to evaluate hepatic events are outlined in Section 10.5 Appendix 5.

The Sponsor should be notified and pirtobrutinib interrupted until the liver function returns to baseline if a patient experiences elevated AST/ALT and bilirubin that meet the following criteria:

- For patients enrolled with normal liver function at baseline, a dose interruption should be implemented if AST or ALT is $>3 \times$ ULN with total bilirubin $2 \times$ ULN without elevation of alkaline phosphatase (ALP) or if AST or ALT is $\geq 5 \times$ ULN.
- For patients enrolled with abnormal liver function at baseline (aspartate aminotransferase [AST] and/or alanine aminotransferase [ALT] $\geq 1.5 \times$ ULN at baseline), a dose interruption should be implemented if AST or ALT is $\geq 3 \times$ baseline or if AST or ALT is $\geq 2 \times$ baseline with concurrent total bilirubin $\geq 2 \times$ ULN.

These patients should undergo a repeat of liver testing (Section 10.4), including ALT, AST, ALP, total bilirubin, and direct bilirubin within 2 to 4 days to confirm the abnormality and to determine if it is increasing or decreasing.

If the abnormality persists or worsens, further clinical and laboratory monitoring and evaluation, for possible causes of abnormal liver tests, should be initiated by the Investigator and possibly in collaboration with a hepatobiliary consultation as clinically appropriate. At a minimum, this evaluation should include a physical examination, a thorough medical history (including symptoms and recent illness), a history of concomitant medications (including over-the-counter and herbal preparations and dietary supplements), and a history of drug and alcohol use. In addition, a blood test for PT-INR should be obtained. Additional laboratory examinations (including, for example, serological tests for viral hepatitis A, B, C, and E) should also be considered.

Based on the patient's history and initial evaluation results, further testing should be considered, in consultation with the Lilly designated medical monitor, including tests for hepatitis D virus, CMV, Epstein-Barr virus, acetaminophen levels, acetaminophen protein adducts, urine toxicology screen, Wilson's disease, blood alcohol levels, urinary ethyl glucuronide, and blood phosphatidylethanol. Based on the circumstances and the investigator's assessment of the participant's clinical condition, the investigator should consider referring the study participant for a hepatologist or gastroenterologist consultation for recommendations concerning further testing (e.g., magnetic resonance cholangiopancreatography, endoscopic retrograde

cholangiopancreatography, abdominal imaging studies (e.g., ultrasound), cardiac echocardiogram, and/or a liver biopsy.)

For the comparator study medications, hepatic safety monitoring should be performed in accordance with their individual product label.

8.5. Unscheduled Visit

All study assessments and procedures will be conducted in accordance with the SoAs. Additional assessments and procedures may be clinically indicated for safety or disease evaluation at the discretion of the Investigator or Sponsor. Any clinically significant indicated assessment or procedure, such as sample blood collection, that is not done in accordance with the SoAs should be reported as an Unscheduled Visit. Documentation, including the reason for the unscheduled visit, must be supported by an entry in the patient's source medical records.

8.6. Adverse Events and Serious Adverse Events

An AE is any unfavorable medical occurrence in a patient administered an investigational product, which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of the investigational product, whether or not considered related to the investigational product.

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments, for example, ECG, radiological scans, and vital sign measurements, including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator, that is, not related to progression of underlying disease.
- Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.
- New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Medication error, misuse, or abuse of IMP, including signs, symptoms, or clinical sequelae.

All AE/SAEs that occur prior to the first dose are considered medical history unless the AE develops or worsens due to study related procedures. All SAEs that occurred from the time of the start of treatment to SFU (28 days [+ 7 days] after the last dose of the study drug) are to be reported to Sponsor and recorded on the appropriate eCRF. However, if an SAE occurs after signing the ICF, but prior to receiving the investigational product, the SAE should only be reported if it is considered related to the study procedure. All SAEs that the Investigator considers related to the study drug occurring after the SFU visit must also be reported to the Sponsor. Documentation must be supported by an entry in the patient's source medical records.

Laboratory test abnormalities considered by the Investigator to be clinically relevant should be reported in the eCRF as an AE. Each AE is to be evaluated for duration, severity, and causal relationship with the investigational product or other factors.

Disease progression of the primary tumor in and of itself is captured as an efficacy assessment and should not be captured as an AE (including fatal AEs). If toxicities due to PD exist, and are new or worsened from baseline, these should be reported as AEs. If a new primary malignancy appears, it will also be considered an AE.

Lymphocytosis associated with BTK inhibitor treatment is a well-documented on-target effect and should only be considered an AE if clinically significant.

An overdose in and of itself is not considered an adverse event. However, if a patient who experiences an overdose has signs and symptoms that meet any AE or SAE criterion, this must be reported in the appropriate manner and timeframe and must be documented as clinical sequelae of an overdose.

A DMC is established to oversee the safety aspects of the study. Refer to Section 9.6.

The event term of ‘death’ itself should not be reported as an AE; rather, any AEs associated with the occurrence of death or AEs considered to be Grade 5 in severity (fatal) should be reported.

8.6.1. Grading and Intensity of Adverse Events

The Investigator will grade the severity of each AE using, when applicable, the NCI CTCAE, v5.0. In the event of an AE for which no grading scale exists, the Investigator will classify the AE as mild, moderate, severe, life-threatening/debilitating, or fatal, as defined below.

- Grade 1 mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated. interfering with normal activities.
- Grade 2 moderate; minimal, local or non-invasive intervention indicated; limiting age appropriate instrumental activities of daily living (ADL).
- Grade 3 severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
- Grade 4 life-threatening* consequences; urgent intervention indicated.
- Grade 5 death related to AE.

**Life-threatening:* an AE that places the patient at immediate risk of death. It does not include an adverse reaction that, had it occurred in a more severe form, might have caused death.

Laboratory values which meet Grade 4 NCI CTCAE v5.0 severity based on numeric value may not necessarily meet life-threatening criteria.

8.6.2. Relationship to Underlying Disease, Other Medical Condition or Concomitant Medications

The Investigator will categorize each AE as to its potential relationship to underlying disease, other medical conditions or concomitant medications using the categories of Yes (causally related) and No (not related) as described in Section 8.6.1 and defined below. The assessment of the relationship of an AE to the underlying disease, other medical conditions, or concomitant medications is a clinical decision based on all available information at the time.

No:

The time course between the occurrence or worsening of the AE and underlying disease, other medical conditions, or concomitant medications indicates an alternative causal relationship (other than study drug) and another cause is considered more likely.

Yes:

The time course between the occurrence or worsening of the AE and the underlying disease, other medical conditions, or concomitant medications is consistent with a causal relationship to study drug and another cause is considered unlikely.

The following factors should also be considered:

- Temporal sequence from treatment with the study drug.
- Preclinical and prior clinical data regarding whether a particular AE could be an effect of the study drug (or class of drug).
- Pharmacology and PK of the investigational product.

An unexpected AE is an experience not previously reported or an AE that occurs with specificity, severity, or frequency that is not consistent with the current pirtobrutinib IB or local labels for rituximab or bendamustine. For contraindications for bendamustine, and rituximab or rituximab's approved biosimilar, refer to local prescribing information.

8.6.3. Serious Adverse Event Reporting

An SAE is any untoward medical occurrence that, at any dose:

- results in death
- is life-threatening
- requires hospitalization or prolongation of existing hospitalization
- results in disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event

Medical or scientific judgment should be exercised in deciding whether reporting is 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 patient or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious.

Any hospital admission with at least one overnight stay will be considered an inpatient hospitalization. However, if institutional guidelines mandate hospitalization for a planned procedure (e.g., transfusion of blood products, such as packed red blood cells (PRBCs), platelets or plasma), the underlying AE requiring intervention should not be reported as an SAE unless it meets other serious criteria. An emergency room visit without hospital admission will not be recorded as an SAE under this criterion, nor will hospitalization for a procedure scheduled or planned. Unexpected complications and/or prolongation of hospitalization that occur during elective surgery should be recorded as AEs and assessed for seriousness. Admission to the hospital for social or situational reasons (i.e., no place to stay, live too far away to come for hospital visits) will not be considered inpatient hospitalizations.

In the event of an accidental or intentional overdose by a patient, the site staff must immediately inform Clinical Safety. The eCRF must be updated to reflect this information. In the event that the overdose is associated with an AE and/or SAE, the 2 events should be linked. In the event an AE and or SAE is associated with an overdose, the AE or SAE form must be completed detailing the event and the overdose details.

8.6.3.1. Serious Adverse Event Reporting – Procedures for Investigators: Initial Report

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will evaluate the reported SAEs, including confirmation of relatedness and assessment of expectedness. The sponsor has processes for safety reports for identification, recording, and expedited reporting of SUSARs according to local regulatory requirements. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.

All SAEs must be reported to Clinical Safety within 24 hours of the knowledge of the occurrence. The SAE reporting to the sponsor begins after the patient has signed the ICF and has received the investigational product. However, if an SAE occurs after signing the ICF, but prior to receiving the investigational product, the SAE should be reported to the Sponsor if it is considered reasonably possibly related to the study procedure as per SAE reporting requirements and timelines. All SAEs that the Investigator considers related to the study drug occurring after the 28-day follow-up period must also be reported to the Sponsor.

To report the SAE, complete the paper SAE form located in the Study Manual. Fax or email the completed paper SAE form to Clinical Safety (the fax number and email address is listed below) within 24 hours of awareness.

Safety Contact Information:

Lilly SAE Reporting – USA

USA Fax: 1-317-453-3402 or 1-866-644-1697

Global Email: mailindata_gsmtindy@lilly.com

Lilly SAE Reporting – Rest of World

Rest of World Fax: + xx 1-866-644-1697

Global Email: mailindata_gsmtindy@lilly.com

The Investigator will be requested to supply detailed information regarding the event. SAEs must also be reported to the IRB/IEC and a copy of that report must be retained at the investigative site and filed in the Investigator Site File in accordance with the requirements of that institution.

Although not considered an AE per se, the Sponsor must be notified of any patient or patient's partner who becomes pregnant during a clinical study (refer to Section 8.6.5).

8.6.4. Serious Adverse Event Follow-up

For all SAEs occurring during the study, the Investigator must submit follow-up reports to the Sponsor regarding the status of the SAE and the patient's subsequent course until the SAE has resolved, or until the condition stabilizes or is deemed chronic (in the case of persistent impairment), or the patient dies.

8.6.5. Pregnancy Reporting

If the patient or partner of a patient participating in the study becomes pregnant during the study or within 1 month of pirtobrutinib or 12 months after the last dose of bendamustine or rituximab, whichever is later, the Investigator should report the pregnancy to Clinical Safety within 24 hours of being notified. Clinical Safety will then forward the Pregnancy form to the Investigator for completion.

A patient becoming pregnant while on study drug will Immediately be withdrawn from the study and early termination study procedures will be performed.

The patient or partner should be followed by the Investigator until completion of the pregnancy. If the pregnancy ends for any reason before the anticipated date, the Investigator should notify Clinical Safety. At the completion of the pregnancy, the Investigator will document the outcome of the pregnancy. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e., postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for reporting an SAE.

8.6.6. Secondary Malignancy Reporting

The Investigator must follow up all patients for up to 5 years since the start of the study medication to monitor for the occurrence of any second primary malignancy event. Second primary malignancy events should be reported to the Sponsor regardless of the seriousness or causal attribution to study medication.

8.6.7. Cardiovascular Events Adjudications

Potential cardiovascular events will be identified by the investigative site or by a medical review conducted by the Sponsor or designee. Additional data about each identified potential event should be provided to the Sponsor via specific event adjudication forms. A blinded external Clinical Event Committee will adjudicate the events in a consistent and unbiased manner. The following are the adverse events that will be adjudicated by an external adjudication committee:

- Hospitalization for Heart Failure and Urgent Heart Failure Visit
- Serious Arrhythmia
- Resuscitated Sudden Death.

The specific instructions will be provided by the Sponsor in separate documents.

8.7. Treatment Overdose

For Arm A, refer to the pirtobrutinib IB for further information, recommendations and guidance.

For Arm B, refer to the local product label for bendamustine or rituximab for available information on the signs, symptoms, and treatment of overdose.

8.8. Pharmacokinetics

At the visits and times specified in the SoA (Section 1.3), blood samples of approximately 2 mL each will be collected to determine the plasma concentrations of pirtobrutinib in Arm A only.

A maximum of 6 samples may be collected at additional time points during the study if warranted and agreed upon between both the Investigator and the Sponsor. Instructions for the collection and handling of blood samples will be provided by the Sponsor. The actual date and time (24-hour clock time) of each sampling and prior dose will be recorded.

Blood for PK assessment will be collected on the first day of each consecutive cycle up to Cycle 6. Samples are to be drawn within 1 hour prior to dose, and exact time of sample collection should be recorded. In addition, time of previous dose should be recorded. Additional PK may also be assessed in patients when considered necessary by the Investigator to understand exposure in relationship to possible safety.

Bioanalytical samples collected to measure investigational product concentration and metabolism and/or protein binding will be retained for a maximum of 2 years following last

patient visit for the study. During this time, samples remaining after the bioanalyses may be used for exploratory analyses, such as metabolism, transport and/or protein binding work.

8.9. Pharmacodynamics

Blood samples will be collected and analyzed to correlate biomarkers with response and outcome.

8.10. Biomarkers

Biomarker research is performed to address questions of relevance to drug disposition, target engagement, mechanism of action, resistance mechanisms, variability of patient response (including safety), and clinical outcome. Sample collection is incorporated into clinical studies to enable examination of these questions through measurement of biomolecules including, but not limited to, deoxyribonucleic acid (DNA), circulating free DNA (cfDNA), RNA, proteins, lipids, and other cellular elements. All samples will be coded with the patient number.

Samples will be retained at a facility selected by the Sponsor for a maximum 15 years after the last patient visit for the study, or for a shorter period if local regulations and IRBs/IECs impose shorter time limits. This retention period enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in the development of pirtobrutinib or after pirtobrutinib becomes commercially available.

8.10.1. Bone Marrow Aspirate and Biopsy

A bone marrow aspirate for complex karyotype analyses and for correlative studies should be collected during Screening in accordance with the SoAs (Section 1.3). The biopsy is required at Screening with aspirate and should also be collected even if it is a dry aspirate. In extenuating circumstances, collection of a bone marrow biopsy and aspirate at Screening may be waived based on approval from the Sponsor if the procedure has occurred within 90 days of the planned date of randomization. For central assessment of CR, bone marrow biopsy and aspirate samples should also be collected in accordance with the SoAs (Section 1.3). However, whenever feasible, response assessment by the Investigator should rely on the local evaluation of the bone marrow. Optional bone marrow biopsy and aspirate samples for confirmation of PD may be collected to establish the criteria of PD per iwCLL 2018 if indicated. Guidance on sample collection and timing is provided in the SoAs (Section 1.3) and the Laboratory Manual.

8.10.2. 17p Deletion

At screening, a valid FISH result for 17p deletion status from within 6 months of the date ICF was signed must be documented and used for eligibility in accordance with the SoA (Section 1.3). If local results are not available, a sample must be collected for local or central testing to determine eligibility. At C1D1, an additional sample will be collected for exploratory testing in accordance with the SoA (Section 1.3).

8.10.3. Immunoglobulin Heavy Chain Variable Region Gene (IGHV)

A valid result for IGHV mutational status will be used for stratification, and the de-identified report should be available if requested by the Sponsor. If local results are not available, a valid result must be obtained by local or central testing prior to enrollment. At C1D1, an additional sample will be collected for exploratory testing in accordance with the SoA (Section 1.3).

8.10.4. Pathology and Molecular Reports

De-identified pathology report(s) confirming histologic diagnosis and relevant prognostic biomarkers should be submitted, if available in accordance with the SoAs (Section 1.3). In addition, de-identified molecular report(s) indicating mutation status (e.g. TP53) should be provided, if available in accordance with the SoAs (Section 1.3).

8.10.5. Whole Blood Sample for Correlative Studies

Whole blood samples for correlative studies exploratory analysis (Table 3.1) involving, but not limited to, cfDNA analysis, peripheral blood mononuclear cell (PBMC), minimum residual disease (MRD), and CD19+ cell isolations should be collected in accordance with the SoAs (Section 1.3) and Laboratory Manual. Samples can be used for exploratory research (Table 3.1) to- identify early indicators of treatment efficacy, and to identify potential mechanisms of resistance after treatment with pirtobrutinib. The collected samples may also be used for assessment of, but not limited to, BTK/PLCg2 mutation status, IGHV mutation status, 17p deletion status other FISH marker status analyses. Guidance on sample collection and timing is provided in the SoAs (Section 1.3) and the Laboratory Manual.

8.10.6. Saliva for Germline DNA

Saliva for germline DNA should be collected during Screening unless the patient does not consent. This sample may be used to determine the somatic or germline origin of mutations identified from analysis of archival or fresh tumor samples. Refer to the Laboratory Manual for details regarding sampling and submission.

8.11. Immunogenicity Assessments

Not applicable for this Phase 3 protocol.

8.12. Medical Resource Utilization and Health Economics

8.12.1. Patient Reported Outcomes

Patient reported questionnaires will be administered electronically according to the SoA for PROs (Section 1.3.4) in countries where the questionnaires have been translated into the native language of the region and linguistically validated. The PROs will be used to compare changes in CLL/SLL symptoms, physical function, and other health-related quality of life (HRQoL) outcomes between treatment arms, and generate health utility data. Questionnaires will be

administered electronically using a provisioned electronic patient reported outcome (ePRO) device. Paper PRO questionnaires shall not be used. Patients will complete the specified baseline assessments electronically at clinic at C1D1 prior to their first dose of study drug. Subsequent assessments will be completed at home according to the SoA for PROs (Section 1.3.4) to minimize the number of activities required during clinic visits, with the exception of EOT and SFU. At these visits, the site will trigger the specified EOT and SFU assessments on the patient's ePRO device, therefore patients will be asked to bring their device with them for all clinic visits. If possible, baseline (C1D1), EOT, and SFU questionnaire completion should occur prior to extensive interaction with site health practitioners regarding the patient's status, or receipt of laboratory results and/or additional treatments.

While individual patients may vary in their response time, data from prior research among patients with advanced cancers suggest that 20 items can be completed in an average of less than 4 minutes using an electronic device.

8.12.1.1. EORTC QLQ-C30

Health-related quality of life will be assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 Version 3.0 (EORTC QLQ-C30; [Aaronson et al. 1993](#)). At some patient visits the full scale will be administered and at other times, only selected items.

The full EORTC QLQ-C30 self-reported general cancer instrument consists of 30 items covering 3 dimensions regarding the patient's experience in the past 7 days:

- Global health status/quality of life (2 items)
- Functional scales (15 total items addressing either physical, role, emotional, cognitive, or social functioning)
- Symptom scales (13 total items addressing either fatigue, nausea/vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, or financial impact)

8.12.1.2. EORTC IL58: CLL/SLL Symptom Assessment - Supplement

At timepoints where the EORTC QLQ-C30 is being administered, patients will complete the EORTC IL58, a supplemental set of 5 symptom items associated with CLL/SLL: Night sweats, Fever/Chills, and Fatigue as experienced in the last 7 days.

8.12.1.3. EORTC IL19: Physical Function

The EORTC IL19 consists of five items that are identical to the physical functioning score (items 1-5) of the EORTC QLQ-C30. This assessment will be completed by patients at home at time-points in between administration of the full EORTC QLQ-C30 in order to minimize patient burden.

8.12.1.4. EORTC IL87: CLL/SLL Symptom Assessment

The EORTC IL87 consists of 13 symptom items associated with CLL/SLL that are drawn from the EORTC QLQ-C30 (8 items: appetite loss, fatigue, pain, nausea, dyspnea, sleep problems) and EORTC IL58 (5 items: Night sweats, Fever/Chills, and Fatigue) into a single assessment for completion by the patient at home at time-points in between administration of the full EORTC QLQ-C30 and EORTC IL58 in order to minimize patient burden.

8.12.1.5. EQ-5D-5L

Health status will be assessed using the 5-level-EuroQol (EQ-5D-5L; [Janssen et al. 2012](#)). These utility measures are an important input for economic evaluations by global health technology assessment organizations that examine the value of treatment interventions. Patients will complete the 5-dimension (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), 5-level (no problem, slight, moderate, severe, or extreme problem) assessment according to the SoA. Additionally, patients will indicate their current health status by marking on a visual analog scale ranging from 100 (best imaginable health state) to 0 (worst imaginable health state) as of ‘today’. The EQ-5D-5L is designed for self-completion by respondents, is cognitively simple, takes only a few minutes to complete, and will be administered electronically at the study site according to the SoA prior to receiving study treatment.

8.12.1.6. PGIS - Cancer Symptoms

The Patient Global Impression of Severity (PGIS)-Cancer Symptoms is a single-item assessment whereby patients are asked to report the overall severity of their cancer-related symptoms in the past 7 days using a 5-level response scale ranging from “No Symptoms” to “Very Severe”.

8.12.1.7. PGIC - Cancer Symptoms

The Patient Global Impression of Change (PGIC)-Cancer Symptoms is a single-item assessment whereby patients are asked to report the change in overall severity of their cancer-related symptoms from baseline using a 5-level response scale ranging from “Much Better” to “Much Worse”.

8.12.2. Medical Resource Utilization

Medical resource utilization will be collected in the eCRF by the Investigator and study site personnel for all patients throughout the study. Protocol-mandated procedures, tests, and encounters are excluded.

The data collected will include:

- Hospitalization (yes or no) and duration of hospitalization (admission and discharge dates)

- Emergency room visits (yes and number of events, or no)
- Supportive care medications (GCSF use, transfusions)

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

Treatment with pirtobrutinib will provide a clinically meaningful increase in PFS over treatment with bendamustine plus rituximab (BR) (Arm B) in untreated CLL/SLL patients.

9.2. Sample Size Determination

The study is expected to enroll approximately 250 patients. Patients will be randomized in a 1:1 ratio between pirtobrutinib (Arm A) and comparator bendamustine plus rituximab (Arm B). The study is sized to achieve approximately 90% power to detect a targeted hazard ratio (HR) of 0.41 in PFS which, under the model assumptions, translates into a 144% relative improvement in median PFS comparing the pirtobrutinib arm to the comparator arm, at the 2-sided significance level of 0.05.

This sample size calculation was based on a median PFS time of 43 months in the comparator arm. The accrual period is assumed to be approximately 16 months, and a 10% of dropout is assumed by the time of the final PFS analysis.

9.3. Populations for Analyses

For purposes of analysis, the populations are defined as follows:

Table 9.1 Analysis Populations

Population	Description
Intention to treat (ITT)	All randomized patients, even if a patient does not take the assigned treatment, does not receive the correct treatment, or otherwise does not follow the protocol. Patients will be analyzed according to the treatment group they were assigned to regardless of what actual treatment they receive.
Safety	All randomized patients who take at least 1 dose (including a partial dose) of study treatment. Analysis of safety data will be based on the actual treatment a patient received on the first study treatment administration regardless of which treatment they were randomized to receive (“as treated”).

Data collected for Arm B patients who cross over to pirtobrutinib monotherapy may be analyzed and reported as a stand-alone group, independent of Arm A or Arm B.

9.4. Statistical Analyses

One final analysis is planned. The analysis is planned when approximately 53 IRC -assessed PFS events have been observed, which is expected to occur approximately 32 months after the first patient has been randomized, under the assumption of treatment effect and enrollment projection (Section 9.2).

9.4.1. General Statistical Considerations

Statistical analysis of this study will be the responsibility of the Sponsor or its designee.

All tests of treatment effects will be conducted at a 2-sided alpha level of 0.05, unless otherwise stated.

Continuous variables will be summarized using descriptive statistics (i.e., number of patients, mean, median, standard deviation, minimum, and maximum). Categorical variables will be summarized by frequency and its corresponding percentage.

Handling of missing, unused, and spurious data is addressed prospectively in the overall statistical methods described in the SAP, where appropriate. Adjustments to the planned analyses are described in the final CSR.

Any change to the data analysis methods described in the protocol will require an amendment ONLY if it changes a principal feature of the protocol. More details for the analyses will be provided in the Statistical Analysis Plan (SAP). The SAP will be finalized before database lock. Any changes to the methods described in the final SAP will be described and justified in the clinical study report.

9.4.2. Study Endpoints

The primary, secondary and exploratory endpoints are displayed with the objectives for the study in Section 3.

9.4.3. Treatment Group Comparability

9.4.3.1. Patient Disposition

A detailed description of patient disposition will be provided.

9.4.3.2. Patient Characteristics

Patient demographic and baseline characteristics will be summarized using the ITT population. Baseline disease characteristics, prior anticancer therapies, historical illness, and preexisting conditions will also be summarized.

9.4.3.3. Concomitant Medication

A summary of preferred names of concomitant medication by treatment arm by decreasing frequency will be generated.

9.4.3.4. Subsequent Anticancer Therapy

Subsequent anticancer therapy used to treat CLL will be summarized based on line of therapy and type of therapy.

9.4.3.5. Extent of Exposure

The duration on therapy, dose omissions, dose reductions, dose delays, and dose intensity for each drug will be summarized for all treated patients by arms as appropriate.

9.4.4. Efficacy Analyses

All efficacy analyses will be performed using the ITT population, unless otherwise specified.

9.4.4.1. Analysis of Primary Endpoint

The primary efficacy endpoint of PFS is defined as the time from the date of randomization until PD (assessed by the IRC per iwCLL 2018 criteria, Section 10.7, Appendix 7) or death from any cause, whichever occurs first. Patients not meeting these criteria and alive by the analysis data cutoff date will be censored and the detailed censoring rules will be specified in the SAP.

A log-rank test, stratified by the randomization strata, will be used for the primary comparison of PFS. The HR and its 95% confidence interval (CI) will be computed from a stratified Cox regression model. In addition, median PFS and its 95% CI, as well as PFS rates and associated 95% CI at selected timepoints, will be provided using the Kaplan Meier method. Sensitivity analyses for PFS will be described in the SAP.

The final analysis is planned when approximately 53 IRC-assessed PFS events have been observed, which are expected to occur approximately 32 months after the first patient has been randomized under the assumption of treatment effect and enrollment projection (Section 9.2). Superiority for final analyses is anticipated to be assessed at 2-sided alpha level 0.05 (HR = 0.58). No efficacy interim analysis is planned.

9.4.4.2. Analyses of Secondary Endpoints

The SAP will describe the key secondary endpoints to be tested and the statistical methods to be used to ensure an overall 2-sided Type I error at the level of 0.05.

PFS per Investigator assessment is defined as the time from the date of randomization until PD (per iwCLL 2018 criteria, Section 10.7, Appendix 7) or death from any cause, whichever occurs first. Similar censoring rules and analysis methods will be applied as described for PFS per IRC.

Overall response rate (ORR) is defined as the proportion of patients who achieve a BOR of CR, CRi, nPR, or PR at or before the initiation of subsequent anticancer therapy. The ORR, with 95% CI, will be summarized for each treatment arm. ORR will be compared between Arm A and Arm B using a Cochran-Mantel-Haenszel test stratified by the randomization strata. The ORR will be evaluated according to both IRC and Investigator assessment per iwCLL 2018 criteria. ORR

including PR-L assessed by Investigator and IRC will also be analyzed with the same analysis method used for ORR.

Overall survival (OS) is defined as the time from randomization until death from any cause. If the patient is alive or lost to follow-up at the time of data analysis, OS data will be censored on the last date the patient is known to be alive.

Time to next treatment (TTNT) is defined as time from the date of randomization to the date of the initiation of the next systemic anticancer therapy for CLL/SLL or the first dose date of pirtobrutinib for Arm B patients who crossed over to receive pirtobrutinib or death due to any cause, whichever occurred first.

The analysis methods for OS and TTNT will be similar to those described for PFS. Details of the censoring rules for these endpoints will be provided in SAP.

9.4.5. Safety Analyses

Safety data will be summarized for the safety population. The baseline value for the safety analysis is defined as the value collected at the time closest to and before the start of study drug administration.

9.4.5.1. Adverse Events

AEs will be graded by the Investigator according to the NCI CTCAE v5.0 or higher for nonhematologic and hematologic AEs. Each AE verbatim term will be coded to a system organ class and a preferred term using the Medical Dictionary for Regulatory Activities (MedDRA).

All TEAEs will be summarized by treatment arm. AE incidence rates will also be summarized by severity and relationship to study drug.

Grade 3 or Grade 4 TEAEs; TEAEs leading to permanent study drug treatment discontinuation; TEAEs leading to dose modification; serious TEAEs; and TEAEs resulting in death will be summarized by treatment arm.

9.4.5.2. Clinical Laboratory Tests

For gradable clinical laboratory parameters, a summary of worst postbaseline toxicity grade will be provided in the treatment-emergent period by treatment arm and worst toxicity grade. The difference in percentages will be displayed.

Additional safety endpoints including ECOG, vital signs, and weight will be summarized descriptively with further details provided in the SAP.

9.4.6. Pharmacokinetic/Pharmacodynamic Analyses

Pirtobrutinib plasma concentrations will be summarized by descriptive statistics. Additional analysis utilizing the population PK approach may also be conducted if deemed appropriate.

The relationship between pirtobrutinib plasma exposure and selected efficacy and safety outcomes may be explored.

9.4.7. Other Analyses

9.4.7.1. Patient Reported Outcomes and Medical Resource Utilization

For each PRO instrument, percentage compliance will be calculated as the number of completed assessments divided by the number of expected assessments at each time point. Data will be separately summarized using descriptive statistics.

Time to worsening in disease related symptoms and physical functioning will be described using the method of Kaplan-Meier and comparative analyses between the 2 arms using a log-rank test in a manner similar to that described for PFS will be performed. Further details will be provided in the PRO SAP.

Details for each PRO assessment and patient dimension studied, including those intended to evaluate the performance and measurement properties of each assessment, or understand the relationship between PROs and other study outcomes, and exploratory analysis regarding PRO assessment will also be provided in the PRO SAP.

Frequency counts of hospitalizations, emergency room visits, GCSF use, and transfusions will be reported descriptively for each treatment arm.

9.4.7.2. Subgroup Analyses

Details of subgroup analysis will be provided in SAP.

9.4.7.3. Biomarker Analysis

Biomarker results will be summarized and may be analyzed for correlations with clinical outcomes (both efficacy and safety), if feasible.

9.5. Interim Analyses

No interim analysis is planned.

9.6. Data Monitoring Committee

The DMC will review the safety data periodically and provide recommendations according to the DMC charter.

The first safety data review will be performed by the DMC after approximately 50 patients have been randomized and had the opportunity to be treated for approximately 8 weeks. After the first review meeting, the DMC will meet and review data approximately every 6 months and as needed when required by the Sponsor or DMC. Detailed information on the role of the DMC and frequency of meetings will be provided in the DMC charter separate from this protocol. The Medical Monitor will review safety information on an ongoing basis.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines.
- Applicable International Council for Harmonisation (ICH) GCP Guidelines.
- Applicable laws and regulations.
- The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any substantial amendments or addenda and amended ICFs to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study patients.
- The Investigator will be responsible for the following:
 - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
 - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
 - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.
 - Reporting to the sponsor or designee significant issues related to participant safety, participant rights, or data integrity.

10.1.2. Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the patient or his/her legally authorized representative and answer all questions regarding the study.
- Patients must be informed that their participation is voluntary. Patients or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study center.

- The medical record must include a statement that written informed consent was obtained before the patient was enrolled in the study, before initiation of any study-related Screening procedure and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Patients must be re-consented to the most current version of the ICF(s) during their participation in the study.
- Patients must be consented for crossover treatment.
- A copy of the ICF(s) must be provided to the patient or the patient's legally authorized representative and is kept on file.
- Patients who are rescreened are required to sign a new ICF.

10.1.3. Serious Adverse Event Notification to the Institutional Review Board/Independent Ethics Committee

Suspected unexpected serious adverse reactions (SUSARs) will be reported to the IRB/IEC according to their institutional policy by the Investigator or Sponsor (or Sponsor designee) according to country requirements. Copies of each report and documentation of IRB/IEC notification and acknowledgement of receipt will be kept in the Investigator's study file.

10.1.4. Sponsor Safety Reporting to Regulatory Authorities

The Sponsor or its representative is required to report certain study events in an expedited manner to the Food and Drug Administration, the European Medicines Agency's EudraVigilance electronic system according to Directive 2001/20/EC, and to all country Regulatory Authorities where the study is being conducted, according to local applicable regulations.

The following describes the safety reporting timeline requirements for SUSARs and other reportable events:

Immediately and within 7 calendar days:

- Any suspected AE that is associated with the use of the study drug(s), unexpected, and fatal or life-threatening. Follow-up information must be reported in the following 8 days.

Immediately and within 15 calendar days:

- Any suspected AE that is associated with the use of the study drug, unexpected, and serious, but not fatal or life-threatening, and there is evidence to suggest a causal relationship between the study drug and the event.
- Any finding from tests in laboratory animals that suggest a significant risk for human patients, including reports of mutagenicity, teratogenicity, or carcinogenicity.
- Any event in connection with the conduct of the study or the development of the study drug that may affect the safety of the study patients. In addition, periodic safety reporting to regulatory authorities will be performed by the Sponsor or its representative according to national and local regulations.

10.1.5. Data Protection

- Participants will be assigned a unique identifier by the sponsor to protect the participant's personal data. Any participant information, such as records, datasets, or tissue samples that are transferred to the sponsor will contain the identifier only. Participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that the participant's personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent. This is done by the site personnel through the informed consent process.
- The participant must be informed through the informed consent by the site personnel that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The sponsor has processes in place to ensure information security, data integrity, and data protection. These processes address management of data transfer, and prevention and management of unauthorized access, disclosure, dissemination, alteration or loss of information or personal data. These processes include appropriate contingency plan(s) for appropriate and timely response in the event of a data security breach.
- The transfer of personal data is subject to appropriate safeguards through contractual agreements and processes. The sponsor's processes are compliant with local privacy laws and relevant legislations, including the General Data Protection Regulation (GDPR).

10.1.6. Independent Review Committee Structure

The primary endpoint, PFS, will be assessed by IRC. A blinded IRC will consist of independent radiologists to perform response assessments and determination of PD per iwCLL 2018 criteria (Section [10.7](#), [Appendix 7](#)).

10.1.7. Dissemination of Clinical Study Data

Reports

- The sponsor will disclose a summary of study information, including tabular study results, on publicly available websites where required by local law or regulation.
- The summary of results will be posted within the time frame specified by local law or regulation. If the study remains ongoing in some countries and a statistical analysis of an incomplete dataset would result in analyses lacking scientific rigor (for example, underpowered) or compromise the integrity of the overall analyses (for example, trial not yet unblinded), the summary of results will be submitted within 1 year after the end of the study globally or as soon as available, whichever is earlier.

Data

- The sponsor provides access to all individual participant data collected during the trial, after anonymization, with the exception of pharmacokinetic or genetic data.
- Data are available to request 6 months after the indication studied has been approved in the US and EU and after primary publication acceptance, whichever is later. No expiration date of data requests is currently set once data are made available.
- Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data-sharing agreement.
- Data and documents, including the study protocol, statistical analysis plan, clinical study report, and blank or annotated case report forms, will be provided in a secure data-sharing environment for up to 2 years per proposal.
- For details on submitting a request, see the instructions provided at www.vivli.org.

10.1.8. Data Quality Assurance

- All patient data relating to the study will be recorded in the eCRF unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of patients are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for the time period outlined in the Clinical Trial Agreement (CTA) unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

To ensure accurate, complete, and reliable data, the Sponsor or its representatives will do the following:

- Provide instructional material to the study sites, as appropriate
- Provide Sponsor start-up training to instruct the Investigators and study coordinators. This training will give instruction on the protocol, the completion of the eCRFs, and study procedures.
- Make periodic visits to the study site

- Be available for consultation and stay in contact with the study site personnel by e-mail, telephone, and/or fax
- Review and verify data reported to detect potential errors

In addition, the Sponsor or its representatives will periodically check a sample of the patient data recorded against source documents at the study site. The study may be audited by the Sponsor or its representatives and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

The Investigator will keep records of all original source data. This might include laboratory tests, medical records, and clinical notes. If requested, the Investigator will provide the Sponsor, applicable regulatory agencies, and applicable IRBs/IECs with direct access to original source documents.

10.1.9. Data Capture System

The Investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported to the Sponsor.

An electronic data capture (EDC) system will be used in this study for the collection of eCRF data. The Investigator maintains a separate source for the data entered by the Investigator or designee into the Sponsor provided EDC system. The Investigator is responsible for the identification of any data to be considered source and for the confirmation that data reported are accurate and complete by signing the eCRF.

Additionally, ePRO data questionnaires and scales will be directly recorded by the patient, into an instrument (e.g., an electronic device). The ePRO data will serve as the source documentation and the Investigator does not maintain a separate, written or electronic record of these data.

Data collected via the Sponsor-provided data capture system will be stored at a third-party. The Investigator will have continuous access to the data during the study and until decommissioning of the data capture system.

10.1.10. Source Documents

- Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

10.1.11. Study and Site Closure

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

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

Reasons for the early closure of a study site by the Sponsor or Investigator may include, but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of patients by the Investigator
- Discontinuation of further study treatment development

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the patient and assures appropriate patient therapy and/or follow-up.

10.1.11.1. Discontinuation of the Study

The study will be discontinued if the Sponsor judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

10.1.11.2. Discontinuation of Study Sites

Study site participation may be discontinued if the Sponsor, the Investigator, or the IRB/IEC of the study site judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

10.1.11.3. Adjudication Committee

Data on suspected cardiovascular events will be collected, and the events will be adjudicated by an external, independent clinical events committee composed of cardiologists with expertise in adjudicating hospitalization for heart failure and urgent heart failure visits, serious arrhythmia, and resuscitated sudden death.

10.2. Appendix 2: Clinical Laboratory Tests

Clinical Laboratory Tests

Hematology – Local/central laboratory	
Leukocytes (WBC)	Erythrocytes (RBC)
Neutrophils	Hemoglobin (HGB)
Lymphocytes	Hematocrit (HCT)
Monocytes	Platelets (PLT)
Eosinophils	
Serum Quantitative Immunoglobulins – Local laboratory	
IgG	IgM
IgA	
Coagulation – Local laboratory	
PT/INR	PTT/aPTT
Clinical Chemistry – Local laboratory	
Serum concentrations of:	
Sodium chloride	Lactate dehydrogenase (LDH)
Albumin	Uric acid
Glucose (random)	Beta-2 (B2) microglobulin
Magnesium	Total bilirubin
Potassium	Alanine aminotransferase (ALT)
Calcium	Aspartate aminotransferase (AST)
Phosphorous	Alkaline phosphatase
Creatinine	Direct (or indirect) bilirubin
Urinalysis – Local laboratory	
Blood	Protein
Glucose	Specific gravity
Ketones	Urine leukocyte esterase ^a
pH	Color
Bilirubin	Occult blood
Urobilinogen	
Pregnancy Test^b – Local laboratory	
Urine pregnancy test	Serum pregnancy test

^a Urine microscopy may be used in the place of the urine leukocyte esterase assessment to test for the presence of white blood cells (WBCs).

^b For female patients of childbearing potential.

Note: Neutrophils reported by automated differential hematology instruments include both segmented and band forms. When a manual differential is needed to report the neutrophils, the segmented and band forms should be added together and reported on the CRF, unless the CRF specifically provides an entry field for bands.

10.3. Appendix 3: Contraceptive Guidance and Pregnancy Information

Willingness of women of childbearing potential (WOCBP), and their partners, to both observe barrier and highly effective birth control methods as outlined below for the duration of treatment and for 1 month following the last dose of study treatment or 12 months following last dose of rituximab, whichever is later.

WOCBP are defined as women following menarche and who are not postmenopausal (or 2 years of non-therapy-induced amenorrhea or surgically sterile). WOCBP must utilize 2 effective contraception methods with at least 1 form of highly effective contraception method as outlined below. In addition, male partners of WOCBP on-study must use a barrier method (condoms) for the duration of study treatment and for 1 month following the last dose of study treatment or 12 months after the last dose of rituximab.

Male patients enrolled in Arm B with partners who are WOCBP must use a barrier method (condoms) and their partners must also use a highly effective form of contraception as listed below for the duration of treatment and for 12 months after the last dose of rituximab.

Highly effective birth control methods with a failure rate of less than 1% per year when used consistently and correctly are recommended (Clinical Trial Facilitation Group [CTFG 2014]):

- a. Combined estrogen and progestin containing hormonal contraception associated with inhibition of ovulation given orally, intravaginally, or transdermally
- b. Progestin-only hormonal contraception associated with inhibition of ovulation given orally, by injection, or by implant
- c. Intrauterine device (IUD)
- d. Intrauterine hormone-releasing system (IUS)
- e. Bilateral tubal occlusion
- f. Vasectomized partner
- g. Sexual abstinence: Considered a highly effective method only if defined as refraining from heterosexual intercourse during an entire period of risk associated with the study treatment. The reliability of sexual abstinence will be evaluated in relation to the duration of the study and to the usual lifestyle of the patient.

Notes:

- Women with a history of breast cancer may not use hormone containing contraception (a, b, or d). One of the other listed methods above should be selected.
- WOCBP using hormonal contraception methods should also use a barrier method as a second form of contraception.

Birth control methods that are considered unacceptable or insufficient alone for this clinical trial include (CTFG 2014):

- a. Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action
- b. Male or female condom with or without spermicide
- c. Cap, diaphragm or sponge with spermicide
- d. Combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier methods)
- e. Periodic abstinence (calendar, symptothermal, or post-ovulation methods)
- f. Withdrawal (coitus interruptus)
- g. Spermicide only
- h. Lactational amenorrhea method

Notes:

- Condom/diaphragm with spermicide is not adequate alone.
- Women with a history of breast cancer may not use hormone containing contraception (a). One of the other listed methods above should be selected.
- In patients randomized to Arm B, sperm donation and oocyte donation are prohibited throughout the duration of participation in this protocol and for at least 12 months following the last dose of rituximab.

10.4. Appendix 4: Liver Safety

The hepatic monitoring tests will be conducted in accordance with the SoAs (Section 1.3). Selected tests may be obtained in the event of a clinically significant treatment-emergent hepatic abnormality while on study and should be obtained in accordance with local guidelines and/ or as directed by a local hepatologist when appropriate. Studies may be required in follow-up and will be decided upon between the Investigator and Sponsor when appropriate.

Hepatic Monitoring Tests	
Hepatic Hematology	Haptoglobin
HGB	
HCT	Hepatic Coagulation
Erythrocytes (RBC)	Partial thromboplastin time
Leukocytes (WBC)	Prothrombin time, international normalized ratio (INR)
Neutrophils	
Lymphocytes	Hepatic Serologies
Monocytes	Hepatitis A antibody, total
Eosinophils	Hepatitis A antibody, IgM
Basophils	Hepatitis B surface antigen
Platelets	Hepatitis B surface antibody
	Hepatitis B Core antibody
Hepatic Chemistry	Hepatitis C antibody
Total bilirubin	Hepatitis E antibody, IgG
Direct bilirubin	Hepatitis E antibody, IgM
ALP	
ALT	Other Serology Testing
AST	CMV/EBV testing (antibody and/or DNA)
GGT	Recommended Autoimmune Serology
CPK	Anti-nuclear antibody ^a
	Anti-smooth muscle antibody ^a

Note: Neutrophils reported by automated differential hematology instruments include both segmented and band forms. Whenever a manual differential is needed to report the neutrophils, the segmented and band forms should be added together and recorded on the CRF, unless the CRF specifically provides an entry field for bands.

10.5. Appendix 5: Restricted and Prohibited Concomitant Medication

The following tables describe the drug class and associated medications that will be restricted or be used with caution during the study treatment period. Patients who, in the assessment by the Investigator, require the use of any of the prohibited treatments for clinical management should be removed from the study. Refer to Section 6.5 for additional information.

Note: The lists below are not exhaustive. Also refer to:

<http://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm>.

Note: Nonsystemic (e.g., topical creams, eye drops, mouthwashes, etc.) applications are permissible.

Table 10.1 Strong P-gp Inhibitors

Examples of Strong P-gp Inhibitors	
amiodarone	quinidine
carvedilol	ranolazine
clarithromycin	ritonavir
dronedarone	saquinavir and ritonavir
itraconazole	telaprevir
lapatinib	tipranavir and ritonavir
lopinavir and ritonavir	verapamil
propafenone	

Note: The above list is not exhaustive. Also refer to: <https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers>

Table 10.2 P-gp Substrates

Examples of P-gp Substrates	
dabigatran	loperamide
digoxin	verapamil
fexofenadine	

Note: The above list is not exhaustive. Also refer to: <https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers>.

Table 10.3 CYP2C8 Substrates

Examples of CYP2C8 Substrates	
dasabuvir*	repaglinide*
montelukast	rosiglitazone
pioglitazone	selexipag*
pioglitazone	

*Sensitive CYP2C8 substrates.

Note: The above list is not exhaustive. Also refer to: <https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers>.

Table 10.4 Examples of BCRP Substrates

Examples of BCRP Substrates	
rosuvastatin	apixaban
sulfasalazine	

Note: The above list is not exhaustive. Also refer to: <https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers>.

10.6. Appendix 6: Creatinine Clearance Formula

Creatinine clearance (CrCl) will be assessed at the times when blood chemistries are assessed, as outlined in the SoAs (Section 1.3). Patients must have adequate CrCl to be enrolled (refer to Inclusion Criteria, Section 5.1).

Note: This formula has to be used for calculating CrCl from local laboratory results only.

For serum creatinine concentration in mg/dL:

$$\text{CrCl (mL/min)} = \frac{(140 - \text{age}^a) \times (\text{body wt}) \times 0.85 \text{ (if female)}}{\text{serum creatinine (mg/dL)} \times 72}$$

^a Age in years, weight (wt) in kilograms.

Source: [Cockcroft and Gault 1976](#).

10.7. Appendix 7: iwCLL 2018 Response Criteria

Group	Parameter	CR	PR	PD	SD
A	Lymph nodes ^a	None ≥ 1.5 cm	Decrease $\geq 50\%$ (from baseline) ^a	Increase $\geq 50\%$ from baseline or from response	Change of -49% to +49%
	Liver and/or spleen size ^b	Spleen size < 13 cm; liver size normal	Decrease $\geq 50\%$ (from baseline)	Increase $\geq 50\%$ from baseline or from response	Change of -49% to +49%
	Constitutional symptoms	None	Any	Any	Any
	Circulating lymphocyte count	Normal	Decrease $\geq 50\%$ from baseline	Increase $\geq 50\%$ over baseline	Change of -49% to +49%
B	Platelet count	$\geq 100 \times 10^9/L$	$\geq 100 \times 10^9/L$ or increase $\geq 50\%$ over baseline	Decrease of $\geq 50\%$ from baseline secondary to CLL	Change of -49% to +49%
	Hemoglobin	≥ 11.0 g/dL (untransfused and without erythropoietin)	≥ 11.0 g/dL or increase $\geq 50\%$ over baseline	Decrease of ≥ 2 g/dL from baseline secondary to CLL	Increase < 11.0 g/dL or $< 50\%$ over baseline, or decrease < 2 g/dL
	Marrow	Normo-cellular, no CLL cells, no B-lymphoid nodules	Presence of CLL cells, or of B-lymphoid nodules, or not done	Increase of CLL cells by $\geq 50\%$ on successive biopsies	No change in marrow infiltrate

Source: (Hallek et al. 2018).

Abbreviations: CLL = chronic lymphocytic leukemia; CR = complete remission (all of the criteria have to be met); PD = progressive disease (at least 1 of the criteria of group A or group B has to be met); PR = partial remission (for a PR, at least 2 of the parameters of group A and 1 parameter of group B need to improve if previously abnormal; if only 1 parameter of both groups A and B is abnormal before therapy, only 1 needs to improve); SD = stable disease (all of the criteria have to be met; constitutional symptoms alone do not define PD).

- Sum of the products of 6 or fewer lymph nodes (as evaluated by CT scans and physical examination in clinical studies or by physical examination in general practice).
- Spleen size is considered normal if < 13 cm. There is not firmly established international consensus of the size of a normal liver; therefore, liver size should be evaluated by imaging and manual palpation in clinical studies and be recorded according to the definition used in a study protocol.

Note: Response refers to nadir such that increase $\geq 50\%$ from best response (nadir) is considered PD per iwCLL 2018 criteria.

In addition to the CR, PR, PD and SD response definition as listed in the table above, the protocol requires response assessments of CRi, nPR, and PR-L, as explained below:

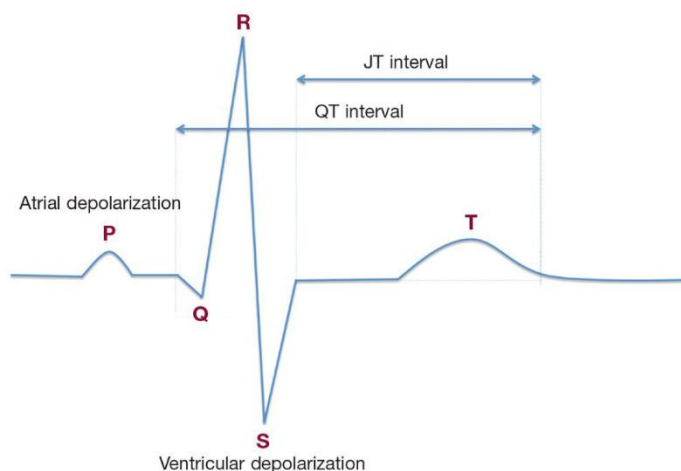
- BTK inhibitors are known to cause lymphocytosis due to redistribution of lymphocytes. In BTK inhibitors or compounds with similar mechanism of action, initial absolute lymphocyte count (ALC) progression with associated PR in other categories during therapy is usually indicative of PR-L (Cheson and Byrd et al. 2012).
- For CRi response, patients must fulfill all criteria for a CR with persistent anemia, neutropenia or thrombocytopenia and the Investigator must attribute these cytopenias as related to investigational drug and not due to the underlying disease.

- For nPR, patients must fulfill all criteria for a CR, but the bone marrow biopsy/aspirate shows B-lymphoid nodules which are evidence for residual disease.

Isolated new lymphocytosis initially occurring during Cycle 1 will not be used as criteria for determining PD.

10.8. Appendix 8: QTcF Measurement Adjustment in Patients with a Widened QRS Complex > 110 ms

The duration of the ECG QT interval reflects the combination of cardiac depolarization which is reflected by the QRS interval and cardiac repolarization, which is defined by the JT interval.



Normal values for the rate-corrected QTc interval are defined largely from populations of patients with normal QRS durations, without bundle branch blocks or intra-ventricular conduction delays. The Fridericia heart rate corrected QTc interval is the most commonly used methodology in drug development, since it usually is the most accurate. In the setting of a widened QRS complex (> 110 ms), however, using the QTcF interval measurement may lead to overestimating cardiac repolarization, since the QTcF would be prolonged due to the contribution from the widened QRS complex; in other words, the QTcF interval could be prolonged despite cardiac repolarization being normal (i.e., a normal JTc interval). For example, if the QRS duration was 150 ms and the QTcF was 500 ms, cardiac repolarization is not meaningfully prolonged when it is considered that a normal QRS duration is conservatively 90 ms. So, in this case, 60 ms (150 ms–90 ms) of the QTcF of 500 ms is due to excessive QRS prolongation and thus the QTcF “adjusted” for the QRS widening is 440 ms (500 ms– [150 ms– 90 ms]).

Thus, for this protocol, in patients with a QRS duration > 110 ms, a QTcF adjusted for the widened QRS duration will be used to assess if a patient meets criteria for protocol exclusion, drug hold, or discontinuation using the below formula:

$$\text{“Adjusted QTcF”} = \text{measured QTcF} - [\text{measured QRS} - 90 \text{ ms}].$$

10.9. Appendix 9: Country-Specific Requirements

The country-specific addenda presented in this appendix must be performed in each of the respective countries, in addition to all procedures required by current version of Protocol J2N-OX-JZNP (JZNP) where applicable. The consolidation of these country-specific addenda into this appendix is to facilitate transition of this trial to the CTIS system under the new clinical trial regulation in Europe.

10.9.1. Addendum 5.0 (Country-Specific Content for Italy)

This addendum is specific to study sites in Italy based on Agenzia Italiana del Farmaco feedback (received on 06 October 2021) on the main study protocol of Study LOXO-BTK-20023.

This addendum amends the study eligibility criteria for patients/subjects enrolled in Italian sites to exclude treatment of autoimmune complications of CLL with rituximab or rituximab biosimilar.

The following table describes the changes being made to the main protocol JZNP for participants in Italy.

Main Protocol Section # and Name	Description of Change
Section 5.2. Exclusion Criteria	To exclude treatment of autoimmune complications of CLL with rituximab or rituximab biosimilar

Country-Specific Protocol Revisions

The following section displays the changes made to protocol conduct within Italy. Changes are shown as strikethrough (i.e., ~~patient~~) for deleted text, and as underscore (i.e., patient) for new/revised text.

Protocol Section 5.2. Exclusion Criteria

[Revised Exclusion Criterion 15; all other criteria remain unchanged and are shown below.]

Medical Conditions

1. Known or suspected Richter's transformation to diffuse large B-cell lymphoma (DLBCL), prolymphocytic leukemia, or Hodgkin lymphoma at any time preceding enrollment.
2. Presence of 17p deletion by fluorescence in-situ hybridization (FISH) (refer to Section 8.10.2)
3. Known or suspected history of central nervous system (CNS) involvement by CLL/SLL.
4. Active second malignancy. Patients with treated second malignancy who are in remission with life expectancy >2 years and with documented Sponsor approval are eligible. Examples include:

- a) Adequately treated non-melanomatous skin cancer or lentigo maligna melanoma without current evidence of disease.
 - b) Adequately treated cervical carcinoma in situ without current evidence of disease.
 - c) Localized (e.g., lymph node negative) breast cancer treated with curative intent with no evidence of active disease present for more than 3 years and receiving adjuvant hormonal therapy.
 - d) Localized prostate cancer undergoing active surveillance.
 - e) History of treated and cured Hodgkin's disease or NHL within 5 years from diagnosis.
5. Major surgery, within 4 weeks of planned start of study treatment.
6. A significant history of renal, neurologic, psychiatric, endocrine, metabolic or immunologic, that, in the opinion of the Investigator, would adversely affect the patient's participation in this study or interpretation of study outcomes.
7. Active uncontrolled auto-immune cytopenia (e.g., autoimmune hemolytic anemia [AIHA], idiopathic thrombocytopenic purpura [ITP]) not on a stable regimen and dose for at least 4 weeks prior to study enrollment
8. Significant cardiovascular disease defined as any of the following:
- a) Unstable angina or acute coronary syndrome within the past 2 months,
 - b) History of myocardial infarction within 3 months prior to planned start of study drug,
 - c) Documented LVEF by any method of $\leq 40\%$
 - d) $\geq$ Grade 3 NYHA functional classification system of heart failure, uncontrolled or symptomatic arrhythmias
9. Prolongation of the QT interval corrected (QTc) for heart rate using Fridericia's Formula (QTcF) > 470 msec on at least 2 of 3 consecutive ECGs, and mean QTcF > 470 msec on all 3 ECGs, during Screening.
- a) QTcF is calculated using Fridericia's Formula ($QTcF = QT/(RR^{0.33})$)
 - b) Correction of suspected drug-induced QTcF prolongation or prolongation due to electrolyte abnormalities can be attempted at the Investigator's discretion, and only if clinically safe to do so with either discontinuation of the offending drug or switch to another drug not known to be associated with QTcF prolongation or electrolyte supplementation.
 - c) Correction of QTc for underlying bundle branch block (BBB) permissible.
10. Hepatitis B or hepatitis C testing indicating active/ongoing infection based on Screening laboratory tests as defined as:
- a) Hepatitis B virus (HBV): Patients with positive hepatitis B surface antigen (HBsAg) are excluded. Patients with positive hepatitis B core antibody (anti-HBc) and negative HBsAg require hepatitis B polymerase chain reaction (PCR) evaluation before randomization. Patients who are hepatitis B PCR positive will be excluded.
 - b) Hepatitis C virus (HCV): positive hepatitis C antibody. If positive hepatitis C antibody result, patient will need to have a negative result for hepatitis C ribonucleic acid (RNA) before randomization. Patients who are hepatitis C RNA positive will be excluded.

c) For optional crossover, repeat testing is not required.

11. Active cytomegalovirus (CMV) infection.
12. Evidence of other clinically significant uncontrolled condition(s) including, but not limited to, uncontrolled systemic infection (viral, bacterial, or fungal) or other clinically significant active disease process which in the opinion of the Investigator and Medical Monitor may pose a risk for patient participation. Screening for chronic conditions is not required.
13. Known Human Immunodeficiency Virus (HIV) infection, regardless of CD4 count. Patients with unknown or negative status are eligible.
14. Clinically significant active malabsorption syndrome or other condition likely to affect gastrointestinal (GI) absorption of the oral administered study treatments.

Prior/Concomitant Therapy

15. Prior systemic therapy for CLL/SLL (except palliative steroids or steroids for treatment of autoimmune complications of CLL ~~with rituximab, rituximab biosimilar, or steroids~~).
16. Concurrent use of investigational agent or anticancer therapy except hormonal therapy.
17. Patients requiring therapeutic anticoagulation with warfarin or another Vitamin K antagonist.
18. Use of ≥ 20 mg prednisone QD or equivalent dose of steroid per day at the time of C1D1. Patients may not be on prednisone of any dose intended for anti-neoplastic use.
19. Vaccination with a live vaccine within 28 days prior to randomization.

Other Exclusions

20. Pregnancy, lactation or plan to breastfeed during the study or within 30 days of the last dose of study treatment.
21. Patients with the following hypersensitivity:
 - a) Known hypersensitivity, including anaphylaxis, to any component or excipient of pirtobrutinib or bendamustine
 - b) Prior significant hypersensitivity to rituximab requiring discontinuation, prior allergic or anaphylactic reaction to rituximab (does not include manageable infusion related reaction)

10.9.2. Addendum 6.0 (Country-Specific Content for Hungary)

This addendum is specific to study sites in Hungary based on feedback from the Medical Research Council Ethics Committee for Clinical Pharmacology (received on 15 October 2021) on the main study protocol of Study LOXO-BTK-20023. This addendum removes the ability to continue treatment beyond progression if the patient is tolerating study treatment and, in the opinion of the Investigator, is deriving ongoing clinical benefit for patients who progress on Arm A.

The following table describes the changes being made to the main protocol JZNP for participants in Hungary.

Main Protocol Section # and Name	Description of Change
1.1. Synopsis – Overall Design	Removes the ability to continue treatment beyond progression if the patient is tolerating study treatment and, in the opinion of the Investigator, is deriving ongoing clinical benefit for patients who progress on Arm A
6.1.2. Arm A Pirtobrutinib: General Dosing Instructions	Removes the ability of patients to continue treatment beyond progression if the patient is tolerating study treatment and, in the opinion of the Investigator, is deriving ongoing clinical benefit for patients who progress on Arm A
6.7.1 Treatment after Progression / Study Completion	Removed text from the title and from first paragraph of Section 6.7.1
7.1. Discontinuation of Study Intervention	Removes the ability of patients to continue treatment beyond progression if the patient is tolerating study treatment

Country-Specific Protocol Revisions

The following section displays the changes made to protocol conduct within Hungary. Changes are shown as strikethrough (i.e., ~~patient~~) for deleted text, and as underscore (i.e., patient) for new/revised text.

Protocol Section 1.1. Synopsis

[Removed text from “Overall Design” sub-section of the Synopsis, as shown below; all other sub-sections of the Synopsis remain unchanged and are not shown.]

Overall Design:

LOXO-BTK-20023 (BRUIN-CLL-313) is a Phase 3 global, randomized, open-label study comparing pirtobrutinib as continuous monotherapy (Arm A) to BR (Arm B) in CLL/SLL patients who are treatment naïve. Patients who are treatment naïve and require therapy per iwCLL 2018 criteria with no evidence of 17p deletion will be enrolled if they meet eligibility criteria. The study will enroll approximately 250 patients and will randomize patients in 1:1 ratio. Patients will be stratified based on immunoglobulin heavy chain variable region gene (IGHV) mutation status (mutated versus unmutated), and on Rai stage (low/intermediate versus high).

This study will enroll adult CLL/SLL patients with an indication for treatment as defined by iwCLL 2018 criteria (Hallek et al. 2018; Cheson et al. 2012; Section 10.6, Appendix 6). Patients assigned to oral pirtobrutinib will receive pirtobrutinib continuously until discontinuation criteria are met (Section 7.1). Patients assigned to BR will receive up to 6 cycles of both agents IV unless they experience unacceptable toxicity or progression, at which time patients will discontinue treatment. Patients who complete the full course of BR or discontinue prior to completing 6 cycles due to intolerance, will be followed until progression, death, lost to follow-up, withdrawal of consent, or study completion. Patients will be allowed to cross over from Arm B to Arm A upon confirmation of radiographic progressive disease (PD) by Independent Review Committee (IRC), and if they meet the eligibility criteria for crossover (Section 5.3). Patients who have PD per the Investigators’ assessment but not IRC, are not eligible for crossover until they meet IRC radiographic PD criteria. ~~Patients who progress on Arm A, may be allowed to continue treatment beyond progression if the patient is tolerating study treatment and, in the opinion of the Investigator, is deriving ongoing clinical benefit. Patients considered for treatment beyond progression must not have symptomatic progression (examples include patients with progression based on lymphocytosis in the absence of evidence of bone marrow failure, or patients with isolated asymptomatic nodal progression). Continuation of treatment on Arm A post progression must be approved by the Sponsor. Patients will need to be consented for treatment beyond progression on pirtobrutinib.~~ Patients who discontinue treatment on either arm for any reason other than PD, death, lost to follow-up, or withdrawal of consent will be followed for tumor assessment until PD, regardless of whether the patient receives a new anticancer therapy. Upon PD, all patients will then be placed on Long-Term Follow-up (LTFU) every 16 weeks for the first 2 years, and every 24 weeks thereafter until death, lost to follow-up, withdrawal of consent, or study completion.

Pirtobrutinib: Patients randomized to Arm A will receive treatment with pirtobrutinib monotherapy.

Bendamustine plus rituximab (BR): Patients randomized to Arm B will receive treatment as outlined below in Study Treatment Groups and detailed in Section 6.1.3.

On days when bendamustine and rituximab are to be administered, rituximab will be administered prior to bendamustine.

Protocol Section 6.1.2. Arm A Pirtobrutinib: General Dosing Instructions

[Removed text from Section 6.1.2, as shown below.]

Each cycle will consist of 28 days. Pirtobrutinib will be given as 200 mg QD administered at approximately the same time on each day (refer to Section 6.1). Dosing of pirtobrutinib is intended to be fixed (i.e., not weight-based- or body surface area [BSA]-based).

Pirtobrutinib may be taken with food or drink. No fasting is required for pirtobrutinib. Refer to Section 6.5 and Section 10.4 (Appendix 4) for concomitant medication considerations.

Patients randomized to pirtobrutinib treatment must keep a daily diary to record dosing compliance of oral study treatment, which will also be assessed at each clinic visit by means of a tablet count in the returned bottle(s). Late doses (i.e., 4 or more hours after scheduled time) should be noted in the diary. Doses that are late by more than 6 hours should not be made up and recorded in the dosing diary as missed. Reasons should be recorded for any missed dose. Vomiting after dosing should be noted in the diary and a vomited dose should not be re-dosed or replaced. Assessment of treatment compliance is described in Section 6.4.

Patients will continue pirtobrutinib dosing until PD, unacceptable toxicity, or other reason for treatment discontinuation. ~~Patients who progress on Arm A, may be allowed to continue treatment beyond progression if the patient is tolerating study treatment and, in the opinion of the Investigator, is deriving ongoing clinical benefit. Patients considered for treatment beyond progression must not have symptomatic progression (examples include patients with progression based on lymphocytosis in the absence of evidence of bone marrow failure, or patients with isolated asymptomatic nodal progression). Continuation of treatment on Arm A post progression must be approved by the Sponsor.~~

Effects of pirtobrutinib on coagulation are unknown. Thus, patients undergoing major surgical procedures should have pirtobrutinib held at least 3 days prior and 3 days post procedure; the Sponsor should be notified of the planned procedure and planned dose hold.

Protocol Section 6.7.1 ~~Treatment after Progression~~ Study Completion

[Removed text from the title and from Section 6.7.1, as shown.]

~~Patients considered for treatment beyond progression must not have symptomatic progression (examples include patients with progression based on lymphocytosis in the absence of evidence of bone marrow failure, or patients with isolated asymptomatic nodal progression).~~

For patients randomized to Arm A: It is anticipated that a patient on this study will receive study treatment with pirtobrutinib until the patient is able to obtain commercially available pirtobrutinib in their respective country, if the patient does not meet criteria requiring discontinuation of treatment, and the patient's participation in the study has not ended. Upon commercial availability in each patient's respective country, there may be additional options for the patient to continue to receive pirtobrutinib once the regulatory requirements are satisfied. These may include, but are not limited to a rollover trial, patient assistance (should the patient qualify), or commercial pirtobrutinib. The study may be terminated if pirtobrutinib does not obtain marketing approval or the development of pirtobrutinib is no longer being pursued by the Sponsor.

For patients receiving Arm B: As study drugs used in Arm B are all locally approved and marketed, the patients on this study treatment may continue treatment as commercially available therapy via physician prescription.

The Sponsor reserves the right to discontinue the study for clinical or administrative reasons at any time.

Protocol Section 7.1. Discontinuation of Study Intervention

[Removed text from Section 7.1, as shown below.]

Patients will be advised that they are free to discontinue study treatment at any time and that they will be followed for survival after discontinuing treatment (refer to Section 6.7.4). Over the course of the study, the Investigator and/or the Sponsor should discontinue a patient from treatment for any of the reasons listed below:

- PD per iwCLL 2018 criteria

~~**Exception:** Patients with documented PD who are tolerating treatment on Arm A and, in the opinion of the Investigator, are deriving clinical benefit from continuing study treatment, may continue treatment with prior Sponsor approval.~~

~~Patients considered for treatment beyond progression must not have symptomatic progression (examples include patients with progression based on lymphocytosis in the absence of evidence of bone marrow failure, or patients with isolated asymptomatic nodal progression).~~

- Unacceptable toxicity
- Intercurrent illness compromising ability to fulfill protocol requirements
- The patient becomes pregnant during the study

- Requirement for alternative treatment in the opinion of the Investigator, unless such treatment is temporary (e.g., local radiation or surgery needed to palliate symptoms of the disease that does not otherwise meet the definition of PD)
- If receiving pirtobrutinib, dose delay > 28 days for hematologic toxicity, unless a clinical need for prolonged delay has been determined by the Investigator with documented Sponsor approval. For Arm B patients with dose delay > 28 days for unacceptable toxicity, consult product package insert.
- Patient is noncompliant, with study procedures and/or treatment upon review with the Sponsor
- Any medical condition that the Investigator determines to be a clinically significant finding which is identified after enrollment and which may jeopardize the patient's safety if study treatment is continued.
- Withdrawal of consent
- Investigator decides that the patient should be discontinued from study treatment.
- Lost to follow-up
- Death
- Study terminated by Sponsor

At the time a patient discontinues treatment, all safety data normally required at the EOT visit will be obtained if possible, as outlined in Section 6.7.3. Patients will enter LTFU where they may be required to undergo disease assessments (refer to Section 6.7.4). Patients who discontinue on Arm B may be considered for crossover to Arm A as determined by eligibility (refer to Section 5.3).

10.9.3. Addendum 7.1 (Country-Specific Content for the Czech Republic)

The following table describes the changes being made to the main protocol JZNP for participants in Czech Republic.

Main Protocol Section # and Name	Description of Change
5.1 Inclusion Criteria	Inclusion criterion #1: Removed requirement that patients be age 18 or older per local regulations at the time of enrollment.
5.2. Exclusion Criteria	Exclusion criterion #13: Edited to remove exception for patients with unknown or negative HIV status
8.4.5.8. Pregnancy Testing	Updated pregnancy testing based on global protocol amendment version
8.4.5.9. Viral Testing	Added HIV testing
8.6.5. Pregnancy Reporting	Updated pregnancy reporting based on global protocol amendment version 3
1.3.1 Schedule of Assessments 1.3.2 Schedule of Assessments 1.3.3 Schedule of Assessments	Updated changes to the Schedule of Assessments based on global protocol amendment version 3

Rationale for Addendum

This addendum is specific to study sites in the Czech Republic based on feedback from the Czech Republic Ministry of Health (Ministerstvo zdravotnictví) (received on 18 October 2021 and 22 November 2021) on the main study protocol of Study LOXO-BTK-20023.

This addendum modifies the protocol in response to requests from the Czech Republic Ministry of Health to 1) change the selected study population to compare with standard treatment according to current knowledge and recommended practices for the BR regimen (i.e., enroll only patients ineligible for fludarabine, cyclophosphamide, and rituximab [FCR], those patients who are > 65 years of age, or ≤ 65 years of age with comorbid conditions as deemed per Investigator's medical judgment), 2) include HIV testing before starting chemoimmunotherapy or treatment with new inhibitors, 3) include more frequent blood counts (monthly) to monitor for incidence of cytopenias, 4) increase the frequency of checks in the Crossover Arm to sufficient intervals (should be as frequent as for Arm A), both for safety monitoring of patients and detection of disease progression, and 5) to harmonize and clarify instructions regarding

pregnancy testing across the protocol and to require pregnancy testing every month with regard to the teratogenicity of the product.

This Addendum 7.1 provides updates to the sections of Pregnancy Testing, Pregnancy Reporting, and the Schedule of Assessments (SoA).

Country-Specific Protocol Revisions

Changes made within the protocol that are applicable to patients in the Czech Republic are shown in the sections below.

Changes are shown as strikethrough (i.e., ~~patient~~) for deleted text, and as underscore (i.e., patient) for new/amended text.

Protocol Section 5.1 Inclusion Criteria

[Revised Criterion 1, as shown.]

Age

1. Fit patients > 65 years of age, or ≤ 65 years of age with comorbid conditions deemed ineligible for fludarabine, cyclophosphamide, and rituximab (FCR). ~~Age 18 years or older per local regulations at time of enrollment.~~

Protocol Section 5.2 Exclusion Criteria

[Revised Criterion 13, as shown.]

Medical Conditions

13. Known Human Immunodeficiency Virus (HIV) infection, regardless of CD4 count.
~~Patients with unknown or negative status are eligible.~~

Protocol Section 8.4.5.8 Pregnancy Testing

[Revised text, as shown.]

For women of childbearing potential (WOCBP): Pregnancy testing (serum or urine) must be conducted at Screening and as outlined in accordance with the SoAs (Section 1.3) or as required per local regulations and/or institutional guidelines and may be performed locally. Pregnancy reporting guidance is provided in Section 8.6.5. WOCBP are defined as women who are following menarche, and who are not postmenopausal (or 2 years of non-therapy-induced amenorrhea) or surgically sterile. For patients in both arms, pregnancy tests must be performed at screening, within 24 hours before C1D1, monthly during treatment, and at EOT and SFU visits. Patients enrolled in Arm B will continue with monthly pregnancy testing during treatment and

for 12 months from the last dose of rituximab. If any urine pregnancy test is positive, study treatment will be delayed until the patient pregnancy status is confirmed by a serum pregnancy test. If serum pregnancy test is positive, the patient will be permanently discontinued from study treatment.

Protocol Section 8.4.5.9 Viral Testing

[Revised second paragraph, as shown.]

Hepatitis testing should be assessed at Screening in accordance with the SoA (Section 1.3) and should include testing for hepatitis B (hepatitis B surface antigen [HBsAg], hepatitis B surface antibody [HBsAb], and total hepatitis B core antibody [HBcAb]) and hepatitis C virus (HCV) antibody serology. Screening for CMV includes IgM, IgG and CMV DNA by PCR. If other testing indicates acute or chronic infection or reactivation of infection, obtain viral load (e.g., quantitative hepatitis B virus [HBV]-DNA, HCV-RNA). Patients with evidence of active hepatitis B and/or hepatitis C infection (as defined in the exclusion criteria) are excluded from participation in the trial.

Patients with known active CMV infection, ~~and/~~ a positive HIV test, or a history of a positive HIV test (regardless of CD4 count) are excluded from participation in the trial due to potential drug-drug interactions between anti-retroviral medications and pirtobrutinib and risk of opportunistic infections with both HIV and approved BTK inhibitors.

Protocol Section 8.6.5 Pregnancy Reporting

[Revised first paragraph, as shown.]

If the patient or partner of a patient participating in the study becomes pregnant during the study or within ~~28 days~~ 1 month of pirtobrutinib ~~study drug~~ or 12 months after the last dose of bendamustine or rituximab, whichever is later, the Investigator should report the pregnancy to Clinical Safety within 24 hours of being notified. Clinical Safety will then forward the Pregnancy form to the Investigator for completion.

A patient becoming pregnant while on study drug will immediately be withdrawn from the study and early termination study procedures will be performed.

The patient or partner should be followed by the Investigator until completion of the pregnancy. If the pregnancy ends for any reason before the anticipated date, the Investigator should notify Clinical Safety. At the completion of the pregnancy, the Investigator will document the outcome of the pregnancy. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e., postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for reporting an SAE.

Schedule of Assessments

Protocol Section 1.3.1 Schedule of Assessments for Arm A: Pirtobrutinib Monotherapy

[Revised rows for “Hematology,” “Hepatitis B/C and HIV active disease status,” and for “Serum or urine pregnancy test (WOCBP only)” and instructions for “documentation of diagnosis and relevant biomarkers,” “17 p deletion evaluation,” “IGHV,” “CMV,” “12 lead ECG,” “blood chemistries,” “coagulation panel,” “urinalysis,” “serum immunoglobulin,” “bone marrow aspirate and biopsy,” “whole blood for correlative studies,” “adverse events,” and “survival status” as shown.]

Schedule of Assessments for Arm A: Pirtobrutinib Monotherapy								
Study Period	Baseline	Study Treatment (Cycle = 28 days)			Post-Study Treatment Discontinuation			Instructions
Evaluation	Screening	Cycle 1	Cycles 2-6	Cycle 7 +	EOT	SFU	LTFU	For Cycle 7, only dispensation of pirtobrutinib will be done at the clinic visit. For Cycle 8, there will be no scheduled clinic visit.
Visit Window	Up to 28 days	Day 1	Day 1 (± 7 days)	Day 1 (± 7 days) Q16W from C1D1 for 2 years and Q24W thereafter	0-7 Days of last dose or decision to terminate treatment	28 Days (+ 7 days) after last dose or decision to terminate treatment	Q16W for first 2 years (relative to C1D1) and Q24W thereafter (± 4 weeks)	An EOT assessment should occur within 7 days of last dose of study treatment or decision to terminate study treatment.
Informed consent	X							The ICF must be signed before any protocol-specified procedures are performed. Refer to Section 10.1.2, Appendix 1
Medical history	X							- All ongoing conditions and relevant past surgical and medical history should be collected. Refer to Section 8.2 - Malignancy history should be collected regarding disease under study, and any history of other malignancy

Schedule of Assessments for Arm A: Pirtobrutinib Monotherapy								
Study Period	Baseline	Study Treatment (Cycle = 28 days)			Post-Study Treatment Discontinuation			Instructions
Evaluation	Screening	Cycle 1	Cycles 2-6	Cycle 7 +	EOT	SFU	LTFU	For Cycle 7, only dispensation of pirtobrutinib will be done at the clinic visit. For Cycle 8, there will be no scheduled clinic visit.
Visit Window	Up to 28 days	Day 1	Day 1 (± 7 days)	Day 1 (± 7 days) Q16W from C1D1 for 2 years and Q24W thereafter	0-7 Days of last dose or decision to terminate treatment	28 Days (+ 7 days) after last dose or decision to terminate treatment	Q16W for first 2 years (relative to C1D1) and Q24W thereafter (± 4 weeks)	An EOT assessment should occur within 7 days of last dose of study treatment or decision to terminate study treatment.
Documentation of diagnosis and relevant biomarkers	X							- De-identified pathology report(s) may be requested to confirm eligibility - Reports regarding status of any known CLL relevant biomarkers should be provided if available (e.g., IGHV, TP53 mutation, complex karyotype, del 11q)

Physical examination	X	X	X	X Q16W from C1D1 for 2 years and Q24W thereafter	X	X	X	- Complete PE includes height (only at Screening), weight, basic neurological examination and review of relevant symptoms at Screening (refer to Section 8.4.2) - Symptom-directed targeted PE should be limited to systems of primary relevance such as, cardiovascular, respiratory, and those associated with tumor assessment (lymph nodes, liver, and spleen) and may be performed at other timepoints; include weight as clinically indicated throughout the trial - Screening results obtained within 3 days of C1D1 are acceptable as C1D1 results - Response assessments include PE (disease and symptom-focused), hematology, and CT or MRI, as described in iwCLL 2018 - PE, hematology, and CT or MRI should occur at indicated intervals relative to C1D1, regardless of any treatment delays or interruptions - For patients who discontinue treatment prior to documented PD, LTFU continues until documented PD, even if started on alternative cancer therapy
ECOG PS	X	X	X	X Q16W from C1D1 for 2 years and Q24W thereafter	X	X		
Vital signs	X	X	X	X Q16W from C1D1 for 2 years and Q24W thereafter	X	X		Includes systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature
Results of tests in the section below are required for eligibility determination and enrollment								
17p deletion evaluation	X	X						- Local 17p deletion results by FISH can be used to determine the eligibility if tested within 6 months of the date ICF was signed - If local 17p deletion results by FISH are not available at Screening, a sample should be

Schedule of Assessments for Arm A: Pirtobrutinib Monotherapy								
Study Period	Baseline	Study Treatment (Cycle = 28 days)			Post-Study Treatment Discontinuation			Instructions
Evaluation	Screening	Cycle 1	Cycles 2-6	Cycle 7 +	EOT	SFU	LTFU	For Cycle 7, only dispensation of pirtobrutinib will be done at the clinic visit. For Cycle 8, there will be no scheduled clinic visit.
Visit Window	Up to 28 days	Day 1	Day 1 (± 7 days)	Day 1 (± 7 days) Q16W from C1D1 for 2 years and Q24W thereafter	0-7 Days of last dose or decision to terminate treatment	28 Days (+ 7 days) after last dose or decision to terminate treatment	Q16W for first 2 years (relative to C1D1) and Q24W thereafter (± 4 weeks)	An EOT assessment should occur within 7 days of last dose of study treatment or decision to terminate study treatment.
								collected and tested locally or centrally prior to enrollment • The C1D1 sample is collected for exploratory purposes
IGHV	X	X						• IGHV results will be used for stratification. When results are not available, a sample should be collected and tested locally or centrally for stratification. • The C1D1 sample is collected for exploratory purposes
CMV	X							CMV IgG, IgM and DNA PCR (Section 8.4.5.5)

Schedule of Assessments for Arm A: Pirtobrutinib Monotherapy								
Study Period	Baseline	Study Treatment (Cycle = 28 days)			Post-Study Treatment Discontinuation			Instructions
Evaluation	Screening	Cycle 1	Cycles 2-6	Cycle 7 +	EOT	SFU	LTFU	For Cycle 7, only dispensation of pirtobrutinib will be done at the clinic visit. For Cycle 8, there will be no scheduled clinic visit.
Visit Window	Up to 28 days	Day 1	Day 1 (± 7 days)	Day 1 (± 7 days) Q16W from C1D1 for 2 years and Q24W thereafter	0-7 Days of last dose or decision to terminate treatment	28 Days (+ 7 days) after last dose or decision to terminate treatment	Q16W for first 2 years (relative to C1D1) and Q24W thereafter (± 4 weeks)	An EOT assessment should occur within 7 days of last dose of study treatment or decision to terminate study treatment.
12-lead ECG	X	X	X	X <u>Q16W from C1D1 for 2 years and Q24W thereafter</u>				Obtain ECGs at specified visits and when patients are symptomatic. Refer to Section 8.4.4. ECGs should be collected: - At Screening, triplicate ECG - C1D1: pre-dose and at 2 hours post dose (single ECG) - If an unscheduled ECG is done at any time, an electrolyte panel (i.e., calcium, magnesium, and potassium) must be done to coincide with the ECG - If a clinically significant arrhythmia is detected, details must be entered in dedicated EDC pages, and the Arrhythmia Collection Form must be sent to the study mailbox
Central hematology		X	C5D1	X Q16W from C1D1 for 2 years and Q24W thereafter	X		X	<u>Testing should be monthly while patient is receiving pirtobrutinib</u> - Includes hemoglobin, hematocrit, RBC, WBC and platelet count, percent or absolute differential (neutrophils, lymphocytes, basophils, eosinophils, and monocytes) - Screening results obtained within 3 days of C1D1 are acceptable as C1D1 results

Schedule of Assessments for Arm A: Pirtobrutinib Monotherapy								
Study Period	Baseline	Study Treatment (Cycle = 28 days)			Post-Study Treatment Discontinuation			Instructions
Evaluation	Screening	Cycle 1	Cycles 2-6	Cycle 7 +	EOT	SFU	LTFU	For Cycle 7, only dispensation of pirtobrutinib will be done at the clinic visit. For Cycle 8, there will be no scheduled clinic visit.
Visit Window	Up to 28 days	Day 1	Day 1 (± 7 days)	Day 1 (± 7 days) Q16W from C1D1 for 2 years and Q24W thereafter	0-7 Days of last dose or decision to terminate treatment	28 Days (+ 7 days) after last dose or decision to terminate treatment	Q16W for first 2 years (relative to C1D1) and Q24W thereafter (± 4 weeks)	An EOT assessment should occur within 7 days of last dose of study treatment or decision to terminate study treatment.
Local hematology	X	X	X	X Monthly	X	X	X	- On days when hematology is required for both safety and response assessments, samples must also be submitted to the central laboratory, including C1D1 - Response assessments include PE (disease and symptom-focused), hematology, and CT or MRI, as described in iwCLL 2018 - PE, hematology, and CT or MRI should occur at indicated intervals relative to C1D1, regardless of any treatment delays or interruptions - For patients who discontinue treatment prior to documented PD, LTFU continues until documented PD, even if started on alternative cancer therapy - Refer to Section 10.2 Appendix 2 Clinical Laboratory Tests
Blood chemistries	X	X	X	X <u>Q16W from C1D1 for 2 years and</u>	X	X		Blood chemistry from serum or plasma should include assessment of: sodium, potassium, chloride, glucose, creatinine, total protein, albumin, total bilirubin, ALT and AST

Schedule of Assessments for Arm A: Pirtobrutinib Monotherapy								
Study Period	Baseline	Study Treatment (Cycle = 28 days)			Post-Study Treatment Discontinuation			Instructions
Evaluation	Screening	Cycle 1	Cycles 2-6	Cycle 7 +	EOT	SFU	LTFU	For Cycle 7, only dispensation of pirtobrutinib will be done at the clinic visit. For Cycle 8, there will be no scheduled clinic visit.
Visit Window	Up to 28 days	Day 1	Day 1 (± 7 days)	Day 1 (± 7 days) Q16W from C1D1 for 2 years and Q24W thereafter	0-7 Days of last dose or decision to terminate treatment	28 Days (+ 7 days) after last dose or decision to terminate treatment	Q16W for first 2 years (relative to C1D1) and Q24W thereafter (± 4 weeks)	An EOT assessment should occur within 7 days of last dose of study treatment or decision to terminate study treatment.
				<u>Q24W thereafter</u>				- In addition, LDH, calcium, magnesium, phosphorus and uric acid are required at Screening and Day 1 of C1 to C6 - Refer to Section 8.4.5.10 for hepatic safety monitoring - Screening results within 3 days of C1D1 are acceptable as C1D1 results - Direct (or indirect) bilirubin should be performed any time total bilirubin is abnormal - Refer to Section 10.2 Appendix 2 Clinical Laboratory Tests
Coagulation panel	X	As clinically indicated						- aPTT and PT (or INR) - Refer to Section 10.2 Appendix 2 Clinical Laboratory Tests
Hepatitis B/C and HIV active disease status	X							- HBV, and HCV, and HIV testing will be used to determine if patients have active infection - Refer to Section 5.2 for exclusions

Schedule of Assessments for Arm A: Pirtobrutinib Monotherapy								
Study Period	Baseline	Study Treatment (Cycle = 28 days)			Post-Study Treatment Discontinuation			Instructions
Evaluation	Screening	Cycle 1	Cycles 2-6	Cycle 7 +	EOT	SFU	LTFU	For Cycle 7, only dispensation of pirtobrutinib will be done at the clinic visit. For Cycle 8, there will be no scheduled clinic visit.
Visit Window	Up to 28 days	Day 1	Day 1 (± 7 days)	Day 1 (± 7 days) Q16W from C1D1 for 2 years and Q24W thereafter	0-7 Days of last dose or decision to terminate treatment	28 Days (+ 7 days) after last dose or decision to terminate treatment	Q16W for first 2 years (relative to C1D1) and Q24W thereafter (± 4 weeks)	An EOT assessment should occur within 7 days of last dose of study treatment or decision to terminate study treatment.
Serum or urine pregnancy test (WOCBP only)	X	X	X	X	X	X		- Perform within 24 hours of first dose of study treatment, and as indicated in table, or as required per local regulations and/or institutional guidelines; refer to Section 10.3 Appendix 3 - Refer to Section 10.2 Appendix 2 Clinical Laboratory Tests - Monthly (Day 1 of each Cycle) from C1D1 until at least 1 month following the last dose of pirtobrutinib
Urinalysis	X	As clinically indicated						- Dipstick analysis is acceptable and should include color, specific gravity, pH, glucose, bilirubin, occult blood, protein, leukocytes, and urobilinogen - Refer to Section 10.2 Appendix 2 Clinical Laboratory Tests
Documentation or sampling of the following are required during Screening, but results <u>not required prior to enrollment</u>								
β2 microglobulin	X							
Serum immunoglobulins	X							- IgG, IgA, IgM - Refer to Section 10.2 Appendix 2 Clinical Laboratory Tests

Schedule of Assessments for Arm A: Pirtobrutinib Monotherapy								
Study Period	Baseline	Study Treatment (Cycle = 28 days)			Post-Study Treatment Discontinuation			Instructions
Evaluation	Screening	Cycle 1	Cycles 2-6	Cycle 7 +	EOT	SFU	LTFU	For Cycle 7, only dispensation of pirtobrutinib will be done at the clinic visit. For Cycle 8, there will be no scheduled clinic visit.
Visit Window	Up to 28 days	Day 1	Day 1 (± 7 days)	Day 1 (± 7 days) Q16W from C1D1 for 2 years and Q24W thereafter	0-7 Days of last dose or decision to terminate treatment	28 Days (+ 7 days) after last dose or decision to terminate treatment	Q16W for first 2 years (relative to C1D1) and Q24W thereafter (± 4 weeks)	An EOT assessment should occur within 7 days of last dose of study treatment or decision to terminate study treatment.
Bone marrow aspirate and biopsy	X		Within 4-8 weeks of confirmed CR by scan and peripheral blood assessment		To confirm PD (optional)			- Refer to Section 8.10.1 - In extenuating circumstances, the requirement for collection of a bone marrow biopsy and aspirate at Screening may be waived based on approval from the Sponsor if the procedure has occurred within 90 days of the planned date of randomization - Whenever feasible, investigator response assessment should rely on local bone marrow results
CT or MRI	X		C5D1	X Q16W from C1D1 for 2 years and Q24W thereafter	X		X	- Refer to Section 8.3.1 for details. - CT scans will be performed every 16 weeks for 2 years and every 24 weeks beyond 2 years; CT scans in between these visits may be performed if PD is suspected - Response assessments include PE (disease and symptom-focused), hematology, and CT or MRI, as described in iwCLL 2018 - PE, hematology, and CT or MRI should occur at indicated intervals relative to C1D1, regardless of any treatment delays or interruptions - For patients who discontinue treatment prior to documented PD, LTFU continues until

Schedule of Assessments for Arm A: Pirtobrutinib Monotherapy								
Study Period	Baseline	Study Treatment (Cycle = 28 days)			Post-Study Treatment Discontinuation			Instructions
Evaluation	Screening	Cycle 1	Cycles 2-6	Cycle 7 +	EOT	SFU	LTFU	For Cycle 7, only dispensation of pirtobrutinib will be done at the clinic visit. For Cycle 8, there will be no scheduled clinic visit.
Visit Window	Up to 28 days	Day 1	Day 1 (± 7 days)	Day 1 (± 7 days) Q16W from C1D1 for 2 years and Q24W thereafter	0-7 Days of last dose or decision to terminate treatment	28 Days (+ 7 days) after last dose or decision to terminate treatment	Q16W for first 2 years (relative to C1D1) and Q24W thereafter (± 4 weeks)	An EOT assessment should occur within 7 days of last dose of study treatment or decision to terminate study treatment.
								documented PD, even if started on alternative cancer therapy • A central radiology vendor will be used to collect and store images for IRC review
Saliva for germline DNA (optional)	X							Collect only if patient has consented to collection and testing; refer to Laboratory Manual for details
Blood samples for PK			X					Pre-dose sample only; refer to Laboratory Manual for details
Whole blood for correlative studies		X	C2D1 and C4D1	X Q16W from C1D1 for 2 years and Q24W thereafter	X		X (Upon confirmation of PD)	• Samples to be provided for exploratory biomarker analyses (Section 8.10.5); refer to Laboratory Manual for details • If a patient discontinues treatment for reasons other than PD, a sample of whole blood should be collected during follow up when PD is confirmed • At the time of bone marrow biopsy to confirm CR, an additional collection of whole blood is required for exploratory biomarker analyses

Schedule of Assessments for Arm A: Pirtobrutinib Monotherapy								
Study Period	Baseline	Study Treatment (Cycle = 28 days)			Post-Study Treatment Discontinuation			Instructions
Evaluation	Screening	Cycle 1	Cycles 2-6	Cycle 7 +	EOT	SFU	LTFU	For Cycle 7, only dispensation of pirtobrutinib will be done at the clinic visit. For Cycle 8, there will be no scheduled clinic visit.
Visit Window	Up to 28 days	Day 1	Day 1 (± 7 days)	Day 1 (± 7 days) Q16W from C1D1 for 2 years and Q24W thereafter	0-7 Days of last dose or decision to terminate treatment	28 Days (+ 7 days) after last dose or decision to terminate treatment	Q16W for first 2 years (relative to C1D1) and Q24W thereafter (± 4 weeks)	An EOT assessment should occur within 7 days of last dose of study treatment or decision to terminate study treatment.
Pirtobrutinib administration								• 200 mg PO administered QD (continuous); refer to Table 6.1 • C1D1 should occur within 7 business days after randomization • Date of last dose and date of decision for end of treatment must be recorded in EDC • Pirtobrutinib will be dispensed at clinic visits for Cycles 1-6, and then Q8W for Cycles 7-24, and then Q12W starting Cycle 25
Patient dosing diary								
Concomitant medication								Refer to Section 6.5

Schedule of Assessments for Arm A: Pirtobrutinib Monotherapy								
Study Period	Baseline	Study Treatment (Cycle = 28 days)			Post-Study Treatment Discontinuation			Instructions
Evaluation	Screening	Cycle 1	Cycles 2-6	Cycle 7 +	EOT	SFU	LTFU	For Cycle 7, only dispensation of pirtobrutinib will be done at the clinic visit. For Cycle 8, there will be no scheduled clinic visit.
Visit Window	Up to 28 days	Day 1	Day 1 (± 7 days)	Day 1 (± 7 days) Q16W from C1D1 for 2 years and Q24W thereafter	0-7 Days of last dose or decision to terminate treatment	28 Days (+ 7 days) after last dose or decision to terminate treatment	Q16W for first 2 years (relative to C1D1) and Q24W thereafter (± 4 weeks)	An EOT assessment should occur within 7 days of last dose of study treatment or decision to terminate study treatment.
Adverse events								- Collect SAEs from the time of ICF signing through SFU. SAEs that occur prior to the first dose are considered medical history unless the SAE develops or worsens due to study-related procedures - All SAEs that the Investigator considers related to the study drug occurring after SFU must be reported to the Sponsor - ALL SAEs must be reported to Clinical Safety within 24 hours of knowledge of the event - Second primary malignancy (SPM) events will continue to be reported up to 5 years since the start of the study drug regardless of the seriousness or causal attribution to treatment (Section 8.6.6) - Collect AEs from the time of dosing through SFU

Schedule of Assessments for Arm A: Pirtobrutinib Monotherapy								
Study Period	Baseline	Study Treatment (Cycle = 28 days)			Post-Study Treatment Discontinuation			Instructions
Evaluation	Screening	Cycle 1	Cycles 2-6	Cycle 7 +	EOT	SFU	LTFU	For Cycle 7, only dispensation of pirtobrutinib will be done at the clinic visit. For Cycle 8, there will be no scheduled clinic visit.
Visit Window	Up to 28 days	Day 1	Day 1 (± 7 days)	Day 1 (± 7 days) Q16W from C1D1 for 2 years and Q24W thereafter	0-7 Days of last dose or decision to terminate treatment	28 Days (+ 7 days) after last dose or decision to terminate treatment	Q16W for first 2 years (relative to C1D1) and Q24W thereafter (± 4 weeks)	An EOT assessment should occur within 7 days of last dose of study treatment or decision to terminate study treatment.
Medical resources utilization								- Hospitalizations, emergency department visits, blood product transfusions, and hematopoietic growth factor use will be collected - Patients (on both treatment arms) need to be assessed Q16W for a total of 2 years, and then Q24W thereafter until PD or 48 months post C1D1 whichever occurs first
Patient reported outcomes								- Refer to Section 1.3.4 for details - Patients (on both treatment arms) need to be assessed according to Section 1.3.4 until PD or 48 months post C1D1 whichever occurs first
Survival status							X	Survival information may be collected via telephone if no procedures are required. Subsequent anticancer therapy information should be collected every 16 weeks for the first 2 years relative to C1D1 and approximately every 24 weeks thereafter until death or study completion

Protocol Section 1.3.2 Schedule of Assessments for Arm B: Bendamustine plus Rituximab (BR)

[Revised rows for “Hematology,” “Hepatitis B/C and HIV active disease status,” “Serum or urine pregnancy test (WOCBP only),” and “17p deletion evaluation” and instructions for “documentation of diagnosis and relevant biomarkers,” “physical examination,” “IGHV,” “CMV,” “12-lead ECG,” “blood chemistries,” “coagulation panel,” “urinalysis,” “serum immunoglobulin,” “bone marrow aspirate and biopsy,” “whole blood for correlative studies,” “adverse events,” and “survival status” as shown.]

Schedule of Assessments for Arm B: Bendamustine plus Rituximab (BR)									
Study Period	Baseline	Study Treatment (Cycle = 28 days)				Post-Study Treatment Discontinuation			Instructions
Evaluation	Screening	Cycle 1		Cycles 2-6		EOT	SFU	LTFU	Patients will proceed to EOT after the Cycle 6 treatment
Visit Window	Up to 28 days	Day 1	Day 2	Day 1 (± 7 days)	Day 2	+ 7 Days of last dose or decision to terminate treatment	28 Days (+ 7 days) after last dose or decision to terminate treatment	Q16W for first 2 years (relative to C1D1) and Q24W thereafter (± 4 weeks)	An EOT assessment should occur within 7 days of last dose of study treatment or decisions to terminate study treatment.
Informed consent	X								The ICF must be signed before any protocol-specified procedures are performed. Refer to Section 10.1.2, Appendix 1
Medical history	X								- All ongoing conditions and relevant past surgical and medical history should be collected. Refer to Section 8.2 - Malignancy history should be collected regarding disease under study, and any history of other malignancy
Documentation of diagnosis and relevant biomarkers	X								- De-identified pathology report(s) may be requested to confirm eligibility - Reports regarding status of any known CLL relevant biomarkers should be provided if available (e.g., IGHV, TP53 mutation, complex karyotype, del 11q)

Schedule of Assessments for Arm B: Bendamustine plus Rituximab (BR)									
Study Period	Baseline	Study Treatment (Cycle = 28 days)				Post-Study Treatment Discontinuation			Instructions
Evaluation	Screening	Cycle 1		Cycles 2-6		EOT	SFU	LTFU	Patients will proceed to EOT after the Cycle 6 treatment
Visit Window	Up to 28 days	Day 1	Day 2	Day 1 (± 7 days)	Day 2	+ 7 Days of last dose or decision to terminate treatment	28 Days (+ 7 days) after last dose or decision to terminate treatment	Q16W for first 2 years (relative to C1D1) and Q24W thereafter (± 4 weeks)	An EOT assessment should occur within 7 days of last dose of study treatment or decisions to terminate study treatment.
Physical examination	X	X		X		X	X	X	- Complete PE includes height (only at Screening), weight, basic neurological examination and review of relevant symptoms at Screening (refer to Section 8.4.2) - Symptom-targeted PE should be limited to systems of primary relevance such as, cardiovascular, respiratory, and those associated with tumor assessment (lymph nodes, liver, and spleen) and may be performed at other timepoints; include weight as clinically indicated throughout the trial - Screening results obtained within 3 days of C1D1 are acceptable as C1D1 results - Response assessments include PE (disease and symptom-focused), hematology, and CT or MRI, as described in iwCLL 2018 - PE, hematology, and CT or MRI should occur at indicated intervals relative to C1D1, regardless of any treatment delays or interruptions - For patients who discontinue treatment prior to documented PD, LTFU continues until documented PD, even if started on alternative cancer therapy
ECOG PS	X	X		X		X	X		

Schedule of Assessments for Arm B: Bendamustine plus Rituximab (BR)									
Study Period	Baseline	Study Treatment (Cycle = 28 days)				Post-Study Treatment Discontinuation			Instructions
Evaluation	Screening	Cycle 1		Cycles 2-6		EOT	SFU	LTFU	Patients will proceed to EOT after the Cycle 6 treatment
Visit Window	Up to 28 days	Day 1	Day 2	Day 1 (± 7 days)	Day 2	+ 7 Days of last dose or decision to terminate treatment	28 Days (+ 7 days) after last dose or decision to terminate treatment	Q16W for first 2 years (relative to C1D1) and Q24W thereafter (± 4 weeks)	An EOT assessment should occur within 7 days of last dose of study treatment or decisions to terminate study treatment.
Vital signs	X	X	X	X	X	X	X		Includes systolic and diastolic blood pressure, heart rate, respiratory rate and body temperature
Results of tests in the section below are required for eligibility determination and enrollment									
17p deletion evaluation	X	X							- Local 17p deletion results by FISH can be used to determine the eligibility if tested within 6 months of the date ICF was signed - If local 17p deletion results by FISH are not available, a sample should be collected and tested locally or centrally prior to enrollment - The C1D1 sample is collected for exploratory purposes
IGHV	X	X							- IGHV results will be used for stratification. When results are not available, a sample should be collected and tested locally or centrally for stratification. - The C1D1 sample is collected for exploratory purposes
CMV	X								CMV IgG, IgM, and DNA PCR (Section 8.4.5.5)
12-lead ECG	X								- Obtain ECGs at specified visit. Refer to Section 8.4.4 - At Screening, triplicate ECG should be collected

Schedule of Assessments for Arm B: Bendamustine plus Rituximab (BR)									
Study Period	Baseline	Study Treatment (Cycle = 28 days)				Post-Study Treatment Discontinuation			Instructions
Evaluation	Screening	Cycle 1		Cycles 2-6		EOT	SFU	LTFU	Patients will proceed to EOT after the Cycle 6 treatment
Visit Window	Up to 28 days	Day 1	Day 2	Day 1 (± 7 days)	Day 2	+ 7 Days of last dose or decision to terminate treatment	28 Days (+ 7 days) after last dose or decision to terminate treatment	Q16W for first 2 years (relative to C1D1) and Q24W thereafter (± 4 weeks)	An EOT assessment should occur within 7 days of last dose of study treatment or decisions to terminate study treatment.
									If a clinically significant arrhythmia is detected, details must be entered in the dedicated EDC pages, and the Arrhythmia Collection Form must be sent to the study mailbox
Local hematology	X	X		X		X	X	X	- Includes hemoglobin, hematocrit, RBC, WBC and platelet count, percent or absolute differential (neutrophils, lymphocytes, eosinophils, and monocytes) - Screening results obtained within 3 days of C1D1 are acceptable as C1D1 results - On days when hematology is required for both safety and response assessments, samples must also be

Schedule of Assessments for Arm B: Bendamustine plus Rituximab (BR)									
Study Period	Baseline	Study Treatment (Cycle = 28 days)				Post-Study Treatment Discontinuation			Instructions
Evaluation	Screening	Cycle 1		Cycles 2-6		EOT	SFU	LTFU	Patients will proceed to EOT after the Cycle 6 treatment
Visit Window	Up to 28 days	Day 1	Day 2	Day 1 (± 7 days)	Day 2	+ 7 Days of last dose or decision to terminate treatment	28 Days (+ 7 days) after last dose or decision to terminate treatment	Q16W for first 2 years (relative to C1D1) and Q24W thereafter (± 4 weeks)	An EOT assessment should occur within 7 days of last dose of study treatment or decisions to terminate study treatment.
Central hematology		X		C5D1		X		X	submitted to the central laboratory, including C1D1 • Response assessments include PE (disease and symptom-focused), hematology, and CT or MRI, as described in iwCLL 2018 • PE, hematology, and CT or MRI should occur at indicated intervals relative to C1D1, regardless of any treatment delays or interruptions • For patients who discontinue treatment prior to documented PD, LTFU continues until documented PD, even if started on alternative cancer therapy • Refer to Section 10.2 Appendix 2 Clinical Laboratory Tests
Blood chemistries	X	X		X		X	X		• Blood chemistry from serum or plasma should include assessment of: sodium, potassium, chloride, glucose, creatinine, total protein, albumin, total bilirubin, ALT and AST • In addition, LDH, calcium, magnesium, phosphorus and uric acid are required at Screening and Day 1 of C1 to C6 • Screening results within 3 days of C1D1 are acceptable as C1D1 results • Refer to Section 10.2 Appendix 2 Clinical Laboratory Tests

Schedule of Assessments for Arm B: Bendamustine plus Rituximab (BR)									
Study Period	Baseline	Study Treatment (Cycle = 28 days)				Post-Study Treatment Discontinuation			Instructions
Evaluation	Screening	Cycle 1		Cycles 2-6		EOT	SFU	LTFU	Patients will proceed to EOT after the Cycle 6 treatment
Visit Window	Up to 28 days	Day 1	Day 2	Day 1 (± 7 days)	Day 2	+ 7 Days of last dose or decision to terminate treatment	28 Days (+ 7 days) after last dose or decision to terminate treatment	Q16W for first 2 years (relative to C1D1) and Q24W thereafter (± 4 weeks)	An EOT assessment should occur within 7 days of last dose of study treatment or decisions to terminate study treatment.
Coagulation panel	X	As clinically indicated							- aPTT and PT (or INR) - Refer to Section 10.2 Appendix 2 Clinical Laboratory Tests
Hepatitis B/C and HIV active disease status	X								- HBV, and HCV, and HIV testing to determine if patients have active infection - Refer to Section 5.2 for exclusions
Serum or urine pregnancy test (WOCBP only)	X	X		X		<u>X</u> <u>Monthly</u> <u>for at least</u> <u>12 months</u> <u>from the</u> <u>last dose of</u> <u>rituximab</u>	X	X	- Perform within 24 hours of first dose of study treatment, and as indicated in table, or as required per local regulations and/or institutional guidelines; refer to Section 10.3 Appendix 3 - Refer to Section 10.2, Appendix 2 Clinical Laboratory Tests
Urinalysis	X	As clinically indicated							- Dipstick analysis is acceptable and should include color, specific gravity, pH, glucose, bilirubin, occult blood, protein, leukocytes, and urobilinogen - Refer to Section 10.2 Appendix 2 Clinical Laboratory Tests

Schedule of Assessments for Arm B: Bendamustine plus Rituximab (BR)									
Study Period	Baseline	Study Treatment (Cycle = 28 days)				Post-Study Treatment Discontinuation			Instructions
Evaluation	Screening	Cycle 1		Cycles 2-6		EOT	SFU	LTFU	Patients will proceed to EOT after the Cycle 6 treatment
Visit Window	Up to 28 days	Day 1	Day 2	Day 1 (± 7 days)	Day 2	+ 7 Days of last dose or decision to terminate treatment	28 Days (+ 7 days) after last dose or decision to terminate treatment	Q16W for first 2 years (relative to C1D1) and Q24W thereafter (± 4 weeks)	An EOT assessment should occur within 7 days of last dose of study treatment or decisions to terminate study treatment.
Documentation or sampling of the following are required during Screening, but results not required prior to enrollment									
β2 microglobulin	X								
Serum immuno-globulins	X								•IgG, IgA, IgM •Refer to Section 10.2 Appendix 2 Clinical Laboratory Tests
Bone marrow aspirate and biopsy	X			Within 4-8 weeks of confirmed CR by scan and peripheral blood assessment		To confirm PD (optional)			• Refer to Section 8.10.1 • In extenuating circumstances, the requirement for collection of a bone marrow biopsy and aspirate at Screening may be waived based on approval from the Sponsor if the procedure has occurred within 90 days of the planned date of randomization • Wherever feasible, response assessment of CR should rely on local bone marrow results
CT or MRI	X			C5D1				X	• Refer to Section 8.3.1 for details. • CT scans will be performed every 16 weeks for 2 years and every 24 weeks beyond 2 years; CT scans in between these visits may be performed if PD is suspected • Response assessments include PE (disease and symptom-focused), hematology, and CT or MRI, as described in iwCLL 2018

Schedule of Assessments for Arm B: Bendamustine plus Rituximab (BR)									
Study Period	Baseline	Study Treatment (Cycle = 28 days)				Post-Study Treatment Discontinuation			Instructions
Evaluation	Screening	Cycle 1		Cycles 2-6		EOT	SFU	LTFU	Patients will proceed to EOT after the Cycle 6 treatment
Visit Window	Up to 28 days	Day 1	Day 2	Day 1 (± 7 days)	Day 2	+ 7 Days of last dose or decision to terminate treatment	28 Days (+ 7 days) after last dose or decision to terminate treatment	Q16W for first 2 years (relative to C1D1) and Q24W thereafter (± 4 weeks)	An EOT assessment should occur within 7 days of last dose of study treatment or decisions to terminate study treatment.
									• PE, hematology, and CT or MRI should occur at indicated intervals relative to C1D1, regardless of any treatment delays or interruptions • For patients who discontinue treatment prior to documented PD, LTFU continues until documented PD, even if started on alternative cancer therapy • A central radiology vendor will be used to collect and store images for IRC review
Saliva for germline DNA (optional)	X								Collect only if patient has consented to collection and testing; refer to Laboratory Manual for details
Whole blood for correlative studies		X		C2D1 and C4D1		X		X (Upon confirmation of PD)	• Samples to be provided for exploratory biomarker analyses (Section 8.10.5); refer to Laboratory Manual for details • If a patient discontinues treatment for reasons other than PD, a sample of whole blood should be collected during follow up when PD is confirmed • At the time of bone marrow biopsy to confirm CR, an additional collection of whole blood is required for exploratory biomarker analyses
Bendamustine administration - IV		90 mg/m ²	90 mg/m ²	90 mg/m ²	90 mg/m ²				• C1D1 should occur within 7 business days after randomization; refer to Table 6.1

Schedule of Assessments for Arm B: Bendamustine plus Rituximab (BR)									
Study Period	Baseline	Study Treatment (Cycle = 28 days)				Post-Study Treatment Discontinuation			Instructions
Evaluation	Screening	Cycle 1		Cycles 2-6		EOT	SFU	LTFU	Patients will proceed to EOT after the Cycle 6 treatment
Visit Window	Up to 28 days	Day 1	Day 2	Day 1 (± 7 days)	Day 2	+ 7 Days of last dose or decision to terminate treatment	28 Days (+ 7 days) after last dose or decision to terminate treatment	Q16W for first 2 years (relative to C1D1) and Q24W thereafter (± 4 weeks)	An EOT assessment should occur within 7 days of last dose of study treatment or decisions to terminate study treatment.
									• Date of last dose and date of decision for end of treatment must be recorded in EDC
Rituximab administration - IV		375 mg/m ²		500 mg/m ² Day 1 of Cycles 2-6					• C1D1 should occur within 7 business days after randomization; refer to Table 6.1 • Date of last dose and date of decision for end of treatment must be recorded in EDC
Concomitant medication									Refer to Section 6.5

Schedule of Assessments for Arm B: Bendamustine plus Rituximab (BR)									
Study Period	Baseline	Study Treatment (Cycle = 28 days)				Post-Study Treatment Discontinuation			Instructions
Evaluation	Screening	Cycle 1		Cycles 2-6		EOT	SFU	LTFU	Patients will proceed to EOT after the Cycle 6 treatment
Visit Window	Up to 28 days	Day 1	Day 2	Day 1 (± 7 days)	Day 2	+ 7 Days of last dose or decision to terminate treatment	28 Days (+ 7 days) after last dose or decision to terminate treatment	Q16W for first 2 years (relative to C1D1) and Q24W thereafter (± 4 weeks)	An EOT assessment should occur within 7 days of last dose of study treatment or decisions to terminate study treatment.
Adverse events									- Collect SAEs from the time of ICF signing through SFU. SAEs that occur prior to the first dose are considered medical history unless the SAE develops or worsens due to study-related procedures - All SAEs that the Investigator considers related to the study drug occurring after the SFU must be reported to the Sponsor - All SAEs must be reported to Clinical Safety within 24 hours of knowledge of the event - Second primary malignancy (SPM) events will continue to be reported up to 5 years since the start of the treatment regardless of the seriousness or casual attribution to treatment (Section 8.6.6) - Collect AEs from the time of dosing through SFU
Medical resources utilization									- Hospitalizations, emergency department visits, blood product transfusions, and hematopoietic growth factor use will be collected - Patients (on both treatment arms) need to be assessed Q16W for a total of 2 years, and then Q24W thereafter until PD or 48 months post C1D1 whichever occurs first

Schedule of Assessments for Arm B: Bendamustine plus Rituximab (BR)									
Study Period	Baseline	Study Treatment (Cycle = 28 days)				Post-Study Treatment Discontinuation			Instructions
Evaluation	Screening	Cycle 1		Cycles 2-6		EOT	SFU	LTFU	Patients will proceed to EOT after the Cycle 6 treatment
Visit Window	Up to 28 days	Day 1	Day 2	Day 1 (± 7 days)	Day 2	+ 7 Days of last dose or decision to terminate treatment	28 Days (+ 7 days) after last dose or decision to terminate treatment	Q16W for first 2 years (relative to C1D1) and Q24W thereafter (± 4 weeks)	An EOT assessment should occur within 7 days of last dose of study treatment or decisions to terminate study treatment.
Patient reported outcomes									- Refer to Section 1.3.4 for details - Patients (on both treatment arms) need to be assessed according to Section 1.3.4 until PD or 48 months post C1D1 whichever occurs first
Survival status								X	Survival information may be collected via telephone if no procedures are required. Subsequent anticancer therapy information should be collected every 16 weeks for the first 2 years relative to C1D1 and approximately every 24 weeks thereafter until death or study completion

Protocol Section 1.3.3 Schedule of Assessments for Optional Crossover Treatment (for patients crossing over from Arm B to Arm A)

[Revised rows for “Hematology,” “ECG,” and for “Serum or urine pregnancy test (WOCBP only)” and instructions for “physical examination,” “hematology,” “blood chemistries,” “coagulation panel,” “urinalysis,” “CT or MRI,” “adverse events,” and “survival status” as shown.]

NOTES:

This SoA is applicable only for patients who were initially randomly assigned to Arm B (BR), and who have PD that is confirmed by the IRC, and who are eligible for crossover (CO) treatment (refer to Section 5.3 Eligibility Criteria for Crossover Treatment), and have elected for optional crossover.

Patients who crossover will complete the Arm B EOT before crossing over to Arm A. Testing and assessments that are performed as part of Arm B, and that are within the Screening window of up to 42 days, do not need to be repeated as a part of the Screening evaluation for crossover.

Schedule of Assessments for Optional Crossover Treatment								
Study Period	Baseline	Study Treatment (Cycle = 28 days)			Post-Study Treatment Discontinuation			Instructions
Evaluation	CO-Screening	CO-Cycle 1	CO-Cycle 4 and higher CO-Cycles 2-6	CO-Cycle 7 +	CO-EOT	CO-SFU	CO-LTFU	
Visit Window	Up to 42 days	Day 1	Day 1 (± 7 days) ± 14 Days	Day 1 (± 7 days)	+14 Days of last dose or decision to terminate treatment	28 Days (+ 7 days) after last dose or decision to terminate treatment	± 4 Weeks	
Informed consent	X							The ICF for crossover must be signed before any protocol-specified procedures are performed. Refer to Section 10.1.2, Appendix 1
Physical examination	X	X	X X Q24W from CO-C1D1	X X Q16W from CO- C1D1 for 2 years and Q24W thereafter	X	X	X	- Complete PE includes height (only at Screening), weight, basic neurological examination and review of relevant symptoms at Screening (refer to Section 8.4.2) - Symptom-targeted targeted PE should be limited to systems of primary relevance such as, cardiovascular, respiratory, and those associated with tumor assessment (lymph nodes, liver, and spleen) and may be performed at other timepoints; include weight as clinically indicated throughout the trial - Screening results obtained within 3 days of CO-C1D1 are acceptable as CO-C1D1 results
ECOG PS	X	X	X X Q24W from CO-C1D1	X X Q16W from CO- C1D1 for 2 years	X	X		

Schedule of Assessments for Optional Crossover Treatment								
Study Period	Baseline	Study Treatment (Cycle = 28 days)			Post-Study Treatment Discontinuation			Instructions
Evaluation	CO-Screening	CO-Cycle 1	CO-Cycles 2-6 CO-Cycle 4 and higher	CO-Cycle 7 +	CO-EOT	CO-SFU	CO-LTFU	
Visit Window	Up to 42 days	Day 1	<u>Day 1</u> <u>(± 7 days)</u> ± 14 Days	<u>Day 1</u> <u>(± 7 days)</u>	+14 Days of last dose or decision to terminate treatment	28 Days (+ 7 days) after last dose or decision to terminate treatment	± 4 Weeks	
				<u>and Q24W thereafter</u>				
Vital signs	X	X	<u>X</u> Q24W from CO-C1D1	<u>X</u> <u>Q16W from CO-C1D1 for 2 years</u> <u>and Q24W thereafter</u>	X	X		• Includes systolic and diastolic blood pressure, heart rate, respiratory rate and body temperature
Results of baseline tests in the section below are required for crossover eligibility determination								
12-lead ECG	X	<u>X</u>	<u>X</u>	<u>X</u> <u>Q16W from CO-C1D1 for 2 years</u> <u>and Q24W thereafter</u>				• Obtain ECGs at specified visits and when patients are symptomatic. Refer to Section 8.4.4 • ECGs should be collected: – At Screening, triplicate ECG – If an unscheduled ECG is done at any time, an electrolyte panel (i.e., calcium, magnesium, and potassium) must be done to coincide with the ECG – If a clinically significant arrhythmia is detected, details must be entered in dedicated EDC pages
Hematology	X	X	<u>X</u>	<u>X</u> <u>Monthly</u>	X	X	<u>X</u> Q24W	• Testing should be <u>monthly while patient is receiving pirtobrutinib</u>

Schedule of Assessments for Optional Crossover Treatment								
Study Period	Baseline	Study Treatment (Cycle = 28 days)			Post-Study Treatment Discontinuation			Instructions
Evaluation	CO-Screening	CO-Cycle 1	CO-Cycles 2-6 CO-Cycle 4 and higher	<u>CO-Cycle 7 +</u>	CO-EOT	CO-SFU	CO-LTFU	
Visit Window	Up to 42 days	Day 1	<u>Day 1</u> (± 7 days) ± 14 Days	<u>Day 1</u> (± 7 days)	+14 Days of last dose or decision to terminate treatment	28 Days (+ 7 days) after last dose or decision to terminate treatment	± 4 Weeks	
			Q24W from CO-C1D1					- Includes hemoglobin, hematocrit, RBC count, WBC count, platelet count, percent or absolute differential (neutrophils, lymphocytes, basophils, eosinophils, and monocytes) - Screening results obtained within 3 days of CO-C1D1 are acceptable as C1D1 results - Refer to Section 10.2 Appendix 2 Clinical Laboratory Tests
Blood chemistries	X	X	Q24W from CO-C1D1 X	<u>X</u> <u>Q16W from CO-C1D1 for 2 years</u> <u>and Q24W thereafter</u>	X	X		- Blood chemistry from serum or plasma should include assessment of: Sodium, potassium, chloride, glucose, creatinine, total protein, albumin, total bilirubin, ALT and AST - In addition, LDH, calcium, magnesium, phosphorus and uric acid are required at Screening and CO-C1D1 and CO-C7D1 - Screening results within 3 days of CO-C1D1 are acceptable as CO-C1D1 results - Direct (or indirect) bilirubin should be performed any time total bilirubin is abnormal - Refer to Section 10.2 Appendix 2 Clinical Laboratory Tests
Coagulation panel	X							Screening and as clinically indicated, aPTT and PT (or INR)

Schedule of Assessments for Optional Crossover Treatment								
Study Period	Baseline	Study Treatment (Cycle = 28 days)			Post-Study Treatment Discontinuation			Instructions
Evaluation	CO-Screening	CO-Cycle 1	CO-Cycles 2-6 CO-Cycle 4 and higher	<u>CO-Cycle 7 +</u>	CO-EOT	CO-SFU	CO-LTFU	
Visit Window	Up to 42 days	Day 1	<u>Day 1</u> (± 7 days) ± 14 Days	<u>Day 1</u> (± 7 days)	+14 Days of last dose or decision to terminate treatment	28 Days (+ 7 days) after last dose or decision to terminate treatment	± 4 Weeks	
								Refer to Section 10.2 Appendix 2 Clinical Laboratory Tests
Serum or urine pregnancy test (WOCBP only)	X	X						- Perform within 24 hours of first dose of study treatment, and as indicated in table, or as required per local regulations and/or institutional guidelines; refer to Section 10.3 Appendix 3 - Refer to Section 10.2 Appendix 2 Clinical Laboratory Tests <u>Monthly (Day 1 of each Cycle) from CO-C1D1 until at least 1 month following the last dose of pirtobrutinib</u>
Urinalysis	X	As clinically indicated						- Dipstick analysis is acceptable and should include color, specific gravity, pH, glucose, bilirubin, occult blood, protein, leukocytes, and urobilinogen - Refer to Section 10.2 Appendix 2 Clinical Laboratory Tests
Documentation or sampling of the following are required during Screening, but results <u>not required prior to initiation of pirtobrutinib</u>								
CT or MRI	X		X Q24W from CO-C1D1	X <u>Q16W from CO-C1D1 for 2 years</u>	X		X Q24W	- Refer to Section 8.3.1 for details. - If baseline CT or MRI assessment documenting PD by IRC was performed within 42 days of

Schedule of Assessments for Optional Crossover Treatment								
Study Period	Baseline	Study Treatment (Cycle = 28 days)			Post-Study Treatment Discontinuation			Instructions
Evaluation	CO-Screening	CO-Cycle 1	CO-Cycle 4 and higher CO-Cycles 2-6	CO-Cycle 7 +	CO-EOT	CO-SFU	CO-LTFU	
Visit Window	Up to 42 days	Day 1	Day 1 (± 7 days) ± 14 Days	Day 1 (± 7 days)	+14 Days of last dose or decision to terminate treatment	28 Days (+ 7 days) after last dose or decision to terminate treatment	± 4 Weeks	
				and Q24W thereafter				planned CO-C1D1, a new scan does not need to be obtained - All response assessments should occur at Q24W intervals relative to CO-C1D1 regardless of any treatment delays or interruptions - Investigator assessment of CT or MRI will be done locally at frequency of at least every 24 weeks or based on standard of care
Pirtobrutinib administration								200 mg PO administered QD (continuous); refer to Table 6.1 - Crossover treatment should be initiated within a window of 42 days after the IRC-confirmed PD - Patient to visit study site Q12W from CO-C4D1 for dispensation of pirtobrutinib - Date of last dose of BR regimen and date of decision to end treatment must be recorded in EDC prior to patient receiving first dose of treatment in crossover
Patient dosing diary								
Concomitant medication								Refer to Section 6.5

Schedule of Assessments for Optional Crossover Treatment								
Study Period	Baseline	Study Treatment (Cycle = 28 days)			Post-Study Treatment Discontinuation			Instructions
Evaluation	CO-Screening	CO-Cycle 1	CO-Cycle 4 and higher CO-Cycles 2-6	CO-Cycle 7 +	CO-EOT	CO-SFU	CO-LTFU	
Visit Window	Up to 42 days	Day 1	Day 1 (± 7 days) ± 14 Days	Day 1 (± 7 days)	+14 Days of last dose or decision to terminate treatment	28 Days (+ 7 days) after last dose or decision to terminate treatment	± 4 Weeks	
Adverse events								- Collect SAEs from the time of ICF signing through CO-SFU. SAEs that occur prior to the first dose are considered medical history unless the SAE develops or worsens due to study-related procedures - All SAEs that the Investigator considers related to the study drug occurring after the CO-SFU must be reported to the Sponsor - All SAEs must be reported to Clinical Safety within 24 hours of knowledge of the event - Collect AEs from the time of dosing through CO-SFU
Survival status							X Q24W	- Survival information may be collected via telephone if no procedures are required. This information should be collected approximately every 24 weeks relative to CO-C1D1; refer to Section 8.3 - Subsequent anticancer therapy information should be collected every 24 weeks relative to CO-C1D1 until death or study completion

10.9.4. Addendum 8.1 (Country-Specific Content for Spain)

The following table describes the changes being made to the main protocol JZNP for participants in Spain.

Main Protocol Section # and Name	Description of Change
3. Objectives and Endpoints	Added safety objective and endpoints to protocol Table 3.1
5.1. Inclusion Criteria	Revised Inclusion Criterion 1, removing “age 18 years or older per local regulations at time of enrollment.”

This addendum is specific to study sites in Spain based on feedback from the Spanish Agency of Medicines and Medicinal Products (AEMPS) on the main study protocol of Study LOXO-BTK-20023. Addendum 8.0 was based on feedback from Spain AEMPS received on 18 November 2021, Addendum 8.1 is based on additional feedback from Spain AEMPS received on 23 December 2021.

This addendum (Addendum 8.1) modifies the protocol in response to requests from Spain AEMPS to add the safety objective and endpoints to Table 3.1 in Section 3 of the current Global Protocol v2.0.

Previously, Addendum 8.0 modified the protocol in response to requests from Spain AEMPS to change the selected study population to compare with standard treatment according to current knowledge and recommended practices for the bendamustine plus rituximab (BR) regimen (i.e., enroll only patients ineligible for fludarabine, cyclophosphamide, and rituximab [FCR], those patients who are > 65 years of age, or 18 to 65 years of age with comorbid conditions as deemed per Investigator’s medical judgment).

Country-Specific Protocol Revisions

Changes made within the protocol that are applicable to patients in Spain are shown below.

Changes are shown as strikethrough (i.e., ~~patient~~) for deleted text, and as underscore (i.e., patient) for new/amended text.

Protocol Section 3. Objectives and Endpoints

[Added safety objective and endpoints to Table 3.1, as shown. This objective/endpoint(s) was included in the table in the Synopsis of the Global Protocol, but was not included in Table 3.1.]

Objectives	Endpoints
Primary	
To evaluate PFS of pirtobrutinib as monotherapy (Arm A) compared to BR (Arm B).	Assessed by IRC: PFS per iwCLL 2018 response criteria
Secondary	
To evaluate the effectiveness of Arm A compared to Arm B based on ORR and time to event(s) outcomes	- Assessed by Investigator: - PFS per iwCLL 2018 criteria - OS - TTNT, defined as time from the date of randomization to the date of the next systemic anticancer therapy for CLL/SLL (see Protocol Section 9 for full definition). - Assessed by Investigator and IRC: - ORR - DOR
<u>To evaluate the safety and tolerability of each treatment arm</u>	<u>Including, but not limited to, serious adverse events (SAEs), adverse events (AEs), deaths and clinical laboratory abnormalities per National Cancer Institute Common Terminology Criteria in Adverse Events v5.0 (NCI CTCAE v5.0)</u>
To evaluate the effectiveness of Arm A compared to Arm B based on patient reported outcomes	- Patient reported outcomes of: - TTW of CLL/SLL-related symptoms - TTW of physical functioning as measured by the physical function domain of the EORTC-QLQ-C30
Tertiary or Exploratory Objectives	
- To identify biomarkers of response and survival in patients treated in both study arms - To identify mechanisms of resistance to pirtobrutinib - To assess use of medical resources including hospitalizations and emergency department visits, transfusions, and growth factor support according to treatment arm - To explore the relationship between pirtobrutinib plasma exposure and selected efficacy and safety outcomes	

Protocol Section 5.1 Inclusion Criteria

[Revised Criterion 1, as shown.]

Age

1. Age > 65 years of age, or 18 to 65 years of age with comorbid conditions deemed ineligible for fludarabine, cyclophosphamide, and rituximab (FCR). ~~Age 18 years or older per local regulations at time of enrollment.~~

10.9.5. Addendum 11.0 (Country-Specific Content for France)

The following table describes the changes being made to the main protocol JZNP for participants in France.

Main Protocol Section # and Name	Description of Change
5.1. Inclusion Criteria	For Inclusion Criterion #1, added text “with comorbid conditions deemed ineligible for fludarabine, cyclophosphamide, and rituximab (FCR), or older than 65 years of age.”
5.2. Exclusion Criteria	For Exclusion Criterion #2 added text “or TP53 mutation (based on local testing).”
1.3.1. Schedule of Assessments for Arm A: Pirtobrutinib Monotherapy	For TP53 line item, added instructional text in the comment column
1.3.2. Schedule of Assessments for Arm B: Bendamustine plus Rituximab (BR)	For TP53 line item, added instructional text in the comment column

Rationale for Addendum

This addendum is specific to study sites in France based on feedback (received at a meeting on 24 November 2021) from the National Agency for the Safety of Medicines and Health Products (ANSM) of France on the main study protocol of Study LOXO-BTK-20023.

This addendum modifies the protocol in response to request from the ANSM of France to restrict criteria to exclude patients with p53 abnormalities who cannot receive fludarabine, cyclophosphamide, and rituximab (FCR) (i.e., the study will enroll only patients ineligible for FCR).

Country-Specific Protocol Revisions

Changes made within the protocol that are applicable to patients in France are shown in the sections below.

Changes are shown as strikethrough (i.e., ~~patient~~) for deleted text, and as underscore (i.e., patient) for new/amended text.

Protocol Section 5.1 Inclusion Criteria

[Revised Criterion 1, as shown.]

1. Age 18 years or older per local regulations at time of enrollment with comorbid conditions deemed ineligible for fludarabine, cyclophosphamide, and rituximab (FCR), or older than 65 years of age.

Protocol Section 5.2 Exclusion Criteria

[Revised Criterion 2, as shown.]

2. Presence of 17p deletion by fluorescence in-situ hybridization (FISH) (refer to Section 8.10.2), or TP53 mutation (based on local testing).

Protocol Section 1.3.1. Schedule of Assessments for Arm A: Pirtobrutinib Monotherapy

[Added row for TP53 testing. Only the revised row is shown below.]

Study Period	Baseline	Study Treatment (Cycle = 28 days)			Post-Study Treatment Discontinuation			Instructions
Evaluation	Screening	Cycle 1	Cycles 2-6	Cycle 7 +	EOT	SFU	LTFU	For Cycle 7, only dispensation of pirtobrutinib will be done at the clinic visit. For Cycle 8, there will be no scheduled clinic visit.
Visit Window	Up to 28 days	Day 1	Day 1 (± 7 days)	Day 1 (± 7 days) Q16W from C1D1 for 2 years and Q24W thereafter	0-7 Days of last dose or decision to terminate treatment	28 Days (+ 7 days) after last dose or decision to terminate treatment	Q16W for first 2 years (relative to C1D1) and Q24W thereafter (± 2 weeks)	An EOT assessment should occur within 7 days of last dose of study treatment or decision to terminate study treatment.
<u>TP53</u>	<u>X</u>							<u>TP53 testing will be done locally. If results of TP53 are available from testing performed prior to signing informed consent, there is no need to repeat testing.</u>

Protocol Section 1.3.2. Schedule of Assessments for Arm B: Bendamustine plus Rituximab (BR)

[Added row for TP53 testing. Only the revised row is shown below.]

Study Period	Baseline	Study Treatment (Cycle = 28 days)				Post-Study Treatment Discontinuation			Instructions
Evaluation	Screening	Cycle 1		Cycles 2-6		EOT	SFU	LTFU	Patients will proceed to EOT after the Cycle 6 treatment
Visit Window	Up to 28 days	Day 1	Day 2	Day 1 (± 7 days)	Day 2	+ 7 Days of last dose or decision to terminate treatment	28 Days (+ 7 days) after last dose or decision to terminate treatment	Q16W for first 2 years (relative to C1D1) and Q24W thereafter (± 2 weeks)	An EOT assessment should occur within 7 days of last dose of study treatment or decisions to terminate study treatment.
<u>TP53</u>	<u>X</u>								<u>TP53 testing will be done locally. If results of TP53 are available from testing performed prior to signing informed consent, there is no need to repeat testing.</u>

10.10. Appendix 10: Abbreviations and Definitions

Term	Definition
abuse	Use of a study intervention for recreational purposes or to maintain an addiction or dependence
ADL	activities of daily living
AE	adverse event: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
AIHA	autoimmune hemolytic anemia [AIHA], idiopathic thrombocytopenic purpura [ITP]
ALC	absolute lymphocyte count
ALP	Alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ATP	adenosine triphosphate
AUC	area under the concentration versus time curve
authorized IMP	<i>Applicable to the EU only:</i> a medicinal product authorized in accordance with Regulation (EC) No 726/2004 or in any Member State concerned in accordance with Directive 2001/83/EC, irrespective of changes to the labelling of the medicinal product, which is used as an investigational medicinal product
authorized AxMP	<i>Applicable to the EU only:</i> a medicinal product authorized in accordance with Regulation (EC) No 726/2004, or in any Member State concerned in accordance with Directive 2001/83/EC, irrespective of changes to the labelling of the medicinal product, which is used as an auxiliary medicinal product
AxMP	Auxiliary medicinal product. See also NIMP. A medicinal product used for the needs of a clinical trial as described in the protocol, but not as an investigational medicinal product. Examples include rescue medication, challenge agents, agents to assess endpoints in the clinical trial, or background treatment. AxMP does not include investigational medicinal product (IMP) or concomitant medications. Concomitant medications are medications unrelated to the clinical trial and not relevant for the design of the clinical trial
BBB	bundle branch block
BCR	B cell receptor
BCL2	B cell lymphoma 2
BID	twice a day
BOR	best overall response
BR	bendamustine with rituximab
BSA	body surface area
BTK	Bruton's tyrosine kinase
C1D1	Cycle 1 Day 1
C1D2	Cycle 1 Day 2
C1D8	Cycle 1 Day 8
C1D15	Cycle 1 Day 15

Term	Definition
C481	cysteine residue at position 481
CAP	College of American Pathologists
CAR-T	chimeric antigen receptor-modified T cells
cfDNA	circulating free DNA
CFR	Code of Federal Regulations
CI	confidence interval
CIT	chemoimmunotherapy
CLIA	Clinical Laboratory Improvement Amendments
CLL/SLL	chronic lymphocytic leukemia/small lymphocytic lymphoma
C_{max}	maximum drug concentration
CMV	cytomegalovirus
CNS	central nervous system
CO	crossover
COPD	chronic obstructive pulmonary disease
CPK	creatine phosphokinase
CR	complete remission
CrCl	creatinine clearance
CT	computed tomography
CTA	Clinical Trial Agreement
CTCAE	Common Terminology Criteria in Adverse Events
CTFG	Clinical Trial Facilitation Group
CYP	cytochrome P450
CYP3A4	cytochrome P450 3A4
DCR	disease control rate
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DOR	duration of response
EBV	Epstein-Barr virus
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
enroll	The act of assigning a patient to a treatment. Patients who are enrolled in the study are those who have been assigned to a treatment.
enter	patients entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
EORTC	European Organisation for Research and Treatment of Cancer Quality of Life questionnaire
EORTC QLQ-C30 PF	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 Version 3.0
EOT	End of Treatment
ePRO	electronic patient reported outcome
EQ-5D-5L	5-level-EuroQol

Term	Definition
ERK	extracellular signal-regulated kinase
FCR	fludarabine, cyclophosphamide, and rituximab
FDG	fluorodeoxyglucose
GCP	Good Clinical Practice
GCSF	granulocyte-colony-stimulating factor
GDPR	EU General Data Protection Regulation
GI	gastrointestinal
GnRH	gonadotropin-releasing hormone
GVHD	graft versus host disease
HBc	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	Hepatitis B virus
HIV	human immunodeficiency virus
HR	hazard ratio
HRQoL	health-related quality of life
IB	Investigator's Brochure
IC90	90% inhibitory concentration
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IGHV	immunoglobulin heavy chain variable region gene
IMP	Investigational Medicinal Product (see also "investigational product"). A medicinal product which is being tested or used as a reference, including as a placebo, in a clinical trial.
informed consent	A process by which a patient voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the patient's decision to participate. Informed consent is documented by means of a written, signed, and dated informed consent form.
INR	international normalized ratio
interim analysis	An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created/locked.
investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical study, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
IRB	Institutional Review Board
IRC	Independent Review Committee
ISO/IEC	International Organization for Standardization/Independent Ethics Committee (ISO/IEC) with International Electrotechnical Commission
ITP	idiopathic thrombocytopenic purpura

Term	Definition
ITT	intention to treat: The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a patient (i.e., the planned treatment regimen) rather than the actual treatment given. It has the consequence that patient allocated to a treatment group should be followed up, assessed, and analyzed as members of that group irrespective of their compliance to the planned course of treatment.
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous(ly)
iwCLL	International Workshop on Chronic Lymphocytic Leukemia
IWRS	interactive voice/web response system
LDH	lactate dehydrogenase
LDT	lymphocyte doubling time
LHRH	luteinizing hormone-releasing hormone
LTFU	Long-Term Follow-up
LVEF	left ventricular ejection fraction
MAPK	mitogen-activated protein kinase
MCL	mantle cell lymphoma
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
medication error	Errors in the prescribing, dispensing, or administration of a study intervention, regardless of whether or not the medication is administered to the participant or the error leads to an AE. Medication error generally involves a failure to uphold one or more of the five “rights” of medication use: the right participant, the right drug, the right dose, right route, at the right time. In addition to the core five rights, the following may also represent medication errors: • dose omission associated with an AE or a product complaint • dispensing or use of expired medication • use of medication past the recommended in-use date • dispensing or use of an improperly stored medication • use of an adulterated dosage form or administration technique inconsistent with the medication’s labeling, for example, Summary of Product Characteristics, IB, local label, protocol, or • shared use of cartridges or prefilled pens or both.
misuse	Use of a study intervention for self-treatment that either is inconsistent with the prescribed dosing regimen or indication, or both, or is obtained without a prescription
MRD	minimal residual disease
MRI	magnetic resonance imaging
MTD	maximal tolerated dose
MZL	marginal zone lymphoma
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NFAT	nuclear factor of activated T cells

Term	Definition
NF-kB	nuclear factor kappa-light-chain-enhancer of activated B cells
NHL	non-Hodgkin lymphomas
NIMP	Non-investigational Medicinal Product. See AxMP. A medicinal product used for the needs of a clinical trial as described in the protocol, but not as an investigational medicinal product. Examples include rescue medication, challenge agents, agents to assess endpoints in the clinical trial, or background treatment.
ORR	overall response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PCP	<i>Pneumocystis jirovecii pneumonia</i>
PCR	polymerase chain reaction
PD	progressive disease; disease progression
PE	physical exam
PFS	progression-free survival
PGIC	(Patient Global Impression of Change
PGIS	Patient's Global Impression of Severity
P-gp	P-glycoprotein
PI3K	phosphoinositide 3-kinase
PK	pharmacokinetics
PKC	protein kinase C
PLCg2	phospholipase C gamma 2
PO	orally (<i>per os</i>)
PR	partial remission
PRBCs	packed red blood cells
PR-L	partial remission with lymphocytosis
PRO	Patient Reported Outcomes
PT	prothrombin time
Q2W	every 2 weeks
Q4W	every 4 weeks
Q16W	every 16 weeks
Q24W	every 24 weeks
QD	once daily
QTc	corrected QT interval
QTcF	QT interval corrected for heart rate using Fridericia's formula
RBC	red blood cell
REB	Research Ethics Board
RNA	ribonucleic acid
RP2D	recommended Phase 2 dose
r/r	relapsed/refractory
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous

Term	Definition
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
SERD	selective estrogen receptor degrader
SERM	selective estrogen receptor modulator
SFU	Safety Follow-up
SoA	Schedule of Assessments
SRC	Safety Review Committee
SUSAR	suspected unexpected serious adverse reaction Refers to an adverse event that occurs in a clinical trial participant, which is assessed by the sponsor and or study investigator as being unexpected, serious, and as having a reasonable possibility of a causal relationship with the study intervention.
SUV	standardized uptake value
TEAE	Treatment-emergent adverse event: An untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment.
TLS	tumor lysis syndrome
T_{max}	time to maximum plasma concentration
TTNT	time to next treatment
TTW	time to worsening
US	United States
ULN	upper limit of normal
WBC	white blood cells
WHO	World Health Organization
WM	Waldenström's macroglobulinemia
WOCBP	woman of childbearing potential
XLA	X-linked agammaglobulinemia
Xid	X-linked immunodeficiency
Y551	tyrosine residue 551

10.11. Appendix 11: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

Amendment 4.0: (25-Aug-2023)

This amendment is considered to be nonsubstantial.

Overall Rationale for the Amendment:

The primary purpose of this amendment is to incorporate changes to the protocol and to consolidate country-specific requirements into protocol appendix to meet EU CTR 536/2014 requirements.

Section # and Name	Description of Change	Brief Rationale
Title page	Added EU trial number	To align with EU CTR
1.1. Synopsis	Added - EudraCT and EU trial numbers - Study population, and - Ethical considerations of benefit/risk.	
2.2.1. Current Approaches to Initial Therapy of CLL/SLL	Added overall benefit risk conclusion subsection	
6.1. Study Interventions Administered	Added row for study intervention EU authorization and use status to Table 6.1	
	Added packaging and labeling subsection	
8.6. Adverse Events and Serious Adverse Events	Added text for events meeting the AE definition	
8.6.3.1. Serious Adverse Event Reporting – Procedures for Investigators: Initial Report	Added text for reporting SAEs and SUSARs	
9.4.1. General Statistical Considerations	Added text regarding handling missing, unused, and spurious data	

Section # and Name	Description of Change	Brief Rationale
10.1.1. Regulatory and Ethical Considerations	Added final bullet	
10.1.5. Data Protection	Updated text	
10.1.7. Dissemination of Clinical Study Data	Updated text	
10.9 Appendix 9: Country-Specific Requirements	Added appendix to include EU-specific requirements for the following countries: Italy Hungary Czech Republic Spain France	To consolidate country-specific requirements into protocol appendix to meet EU CTR requirements
Appendix 10: Abbreviations and Definitions	Updated	To align with EU CTR
Throughout	Minor grammatical and format edits	For clarity

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