# Title Page



**Protocol Title:**

A Phase 2, Open-Label, Randomized Study Evaluating the Efficacy and Safety of 3 Doses of Pirtobrutinib in Participants with Relapsed or Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Who Previously Received Treatment with a Covalent Bruton Tyrosine Kinase Inhibitor

**Protocol Number:** J2N-MC-JZNX

**Amendment Number:** JZNX (a)

**Compound:** Pirtobrutinib

**Brief Title:**

A Study Evaluating the Efficacy and Safety of Pirtobrutinib in Participants with Relapsed or Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Who Previously Received Treatment with a Covalent Bruton Tyrosine Kinase Inhibitor

**Study Phase:** 2

**Sponsor Name:** LOXO Oncology, Inc

**Legal Registered Address:** Stamford, Connecticut, USA 06901

**Regulatory Agency Identifier Numbers:**

IND: 139876

EU trial number: 2024-515689-15-00

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

**Document ID:** VV-CLIN-142945

**Medical monitor name and contact information will be provided separately.**

# Protocol Amendment Summary of Changes Table

| DOCUMENT HISTORY | |
|---|---|
| **Document** | **Date** |
| Original Protocol | 26 Jun 2024 |

## Amendment (a)

The amendment is considered to be substantial because it is likely to have a significant impact on the safety or the rights of the study participants.

## Overall rationale for the amendment

The overall rationale for this amendment is to address FDA feedback.

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| Section 1.3.1. Schedule of Activities | Removed "V1" for Baseline (Day Relative to C1D1) from SoA table | Editorial error |
| Section 5.2. Exclusion Criteria | Criterion 36: Revised to "Require therapy with a strong CYP3A inhibitor that cannot be stopped within 14 days before the first dose of study intervention."<br>Addition of "See Section 10.8 for examples of excluded medications and suggested alternatives that are not strong CYP3A inhibitors." | To address FDA feedback |
| | Criterion 37: Addition of "See Section 10.8 for examples of excluded medications." | |
| | Added Exclusion Criterion 38 "Require therapy with substrates of P-gp and BCRP that are sensitive to minimal concentration changes. See Section 10.8 for examples of excluded medications." | |
| | The exclusion criteria post criterion 38 were renumbered. | |
| Section 6.6.1. Guidelines for Adjusting or Withholding or Discontinuing Study Intervention to Manage AEs | Added footnotes "b" and "c" to the table to provide additional guidance to dose modifications specific for Grades 3 and 4 treatment-related AEs. | To address FDA feedback |
| Section 6.9.2. Prohibited Concomitant Therapy | Revised the section to clarify which concomitant medications should not be co-administered with pirtobrutinib during the study. | To address FDA feedback |
| Section 6.9.4. Concomitant Use with Medications that are Sensitive P-gp, CYP2C8, or BCRP Substrates | Deleted the entire section. The next section was renumbered. | To address FDA feedback and simplify the protocol |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| Section 10.2. Appendix 2: Clinical Laboratory Tests | Deleted thyroid testing from the list | Editorial error |
| Section 10.8. Appendix 8: Examples of Excluded Medications | A new appendix was added as Appendix 8 to reflect the examples of excluded medications. The existing Appendix 8 was renumbered to Appendix 9. | To address FDA feedback and clarify guidance on prohibited concomitant medications to investigators |
| Section 10.9. Appendix 9: Abbreviations and Definitions | Added “P-gp: permeability glycoprotein” to the list | Addition |
| Throughout | Minor editorial and formatting changes. | Minor, therefore, not detailed |

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# 1. Protocol Summary

## 1.1. Synopsis

**Protocol Title:**

A Phase 2, Open-Label, Randomized Study Evaluating the Efficacy and Safety of 3 Doses of Pirtobrutinib in Participants with Relapsed or Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Who Previously Received Treatment with a Covalent Bruton Tyrosine Kinase Inhibitor

**Brief Title:**

A Study Evaluating the Efficacy and Safety of Pirtobrutinib in Participants with Relapsed or Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Who Previously Received Treatment with a Covalent Bruton Tyrosine Kinase Inhibitor

**Regulatory Agency Identifier Numbers:**

IND: 139876

EU trial number: 2024-515689-15-00

**Rationale:**

This study is an FDA post-marketing requirement (PMR 4557-2) to further assess the efficacy and safety of 3 dose levels of pirtobrutinib in patients with relapsed or refractory chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), who have received 1-3 lines of treatment, including a covalent Bruton tyrosine kinase (BTK) inhibitor.

Although several dose levels were evaluated in the LOXO-BTK-18001 study, relatively few participants were treated at doses lower than 200 mg; thus the need to further explore if a reduced dose could improve the safety profile without compromising efficacy.

**Objectives, Endpoints, and Estimands:**

| Objectives | Endpoints |
|---|---|
| **Primary** | |
| To compare the overall response rate of<br>• pirtobrutinib 200 mg to CCI and<br>• pirtobrutinib 200 mg to CCI | Overall response rate, as assessed by the investigator per iwCLL 2018.<br>Overall response rate is defined as the proportion of participants who achieve the best overall response at or before the initiation of subsequent anticancer therapy of<br>• CR<br>• CRi<br>• nPR, or<br>• PR |
| **Secondary** | |
| To determine the incidence of ≥Grade 3 AESIs that occur at each pirtobrutinib dose level | ≥Grade 3 AESIs |
| To determine the duration of response of each pirtobrutinib dose level | Duration of response.<br>Duration of response is defined as the time from the date of the first documented CR, CRi, nPR, or PR to disease progression (per iwCLL 2018) or death from any cause |
| To determine the safety and tolerability of each pirtobrutinib dose level | Including, but not limited to<br>• ≥Grade 3 TEAEs<br>• SAEs<br>• discontinuations due to an AE<br>• dose interruptions due to an AE, and<br>• dose reductions due to an AE |

Abbreviations: AE = adverse event; AESI = adverse events of special interest; CR = complete remission; CRi = complete remission with incomplete hematologic recovery; iwCLL = International Workshop on Chronic Lymphocytic Leukemia; nPR = nodular partial remission; PR = partial remission; SAE = serious adverse events; TEAE = treatment-emergent adverse events.

**Overall Design:**

This is a Phase 2, open-label, randomized study evaluating the efficacy and safety of different dose levels of pirtobrutinib in participants with relapsed or refractory CLL/SLL, who have received 1-3 lines of treatment, including a covalent BTK inhibitor.

This study will further evaluate the safety, tolerability, and efficacy of 3 different dosages of pirtobrutinib, 200 mg, CCI once daily.

**Brief Summary:**

The start of treatment at Cycle 1 Day 1 (C1D1) should occur within 5 business days after randomization. With sponsor permission, a maximum of 7 additional days delay between randomization and C1D1 may occur due to holiday, weekend, bad weather, or other unforeseen circumstances.

Participants will receive pirtobrutinib continuously in this study until discontinuation criteria are met or criteria are met for the end of study.

**Posttreatment follow-up**

Short-term follow-up begins when the participant and investigator agree that the participant will no longer continue study intervention.

Long-term follow-up begins when the participant completes the short-term follow-up visit and ends with either the end of study, withdrawal of consent, loss to follow-up, or the participant's death, whichever is earlier.

**Study Population:**

In general, an individual may take part in this study if they

- are 18 years of age or older, or are of a legal age in the location in which the study is taking place
- have a confirmed diagnosis of CLL/SLL
- are required to receive treatment for CLL/SLL
- have received at least 1, but not more than 3 lines of, treatment for CLL/SLL and have received a covalent BTK inhibitor as one of those treatments, and
- are able to walk around on their own and take care of themselves.

In general, an individual may not take part in this study if they

- have had another type of cancer in the past 3 years. Exceptions may occur with documented sponsor approval. Examples of exceptions include
    - skin cancer that is not a melanoma
    - abnormal cells in the cervix that have not spread to other parts of the body
    - prostate cancer that was completely inside the prostate gland and did not spread, and
    - breast cancer that did not spread beyond the breast tissue and has not been present for more than 3 years.
- have major surgery planned in the near future
- have a history of significant cardiovascular disease, and

- have certain diseases of the liver or an injured liver due to previous drug treatments.

**Number of Participants:**

Approximately 249 participants will be randomly assigned in a [redacted] ratio to study intervention.

**Intervention Groups and Duration:**

This study will evaluate 3 dose levels of pirtobrutinib, 200 mg, [redacted] once daily.

Participants will receive pirtobrutinib continuously in this study until discontinuation criteria are met or criteria are met for the end of study.

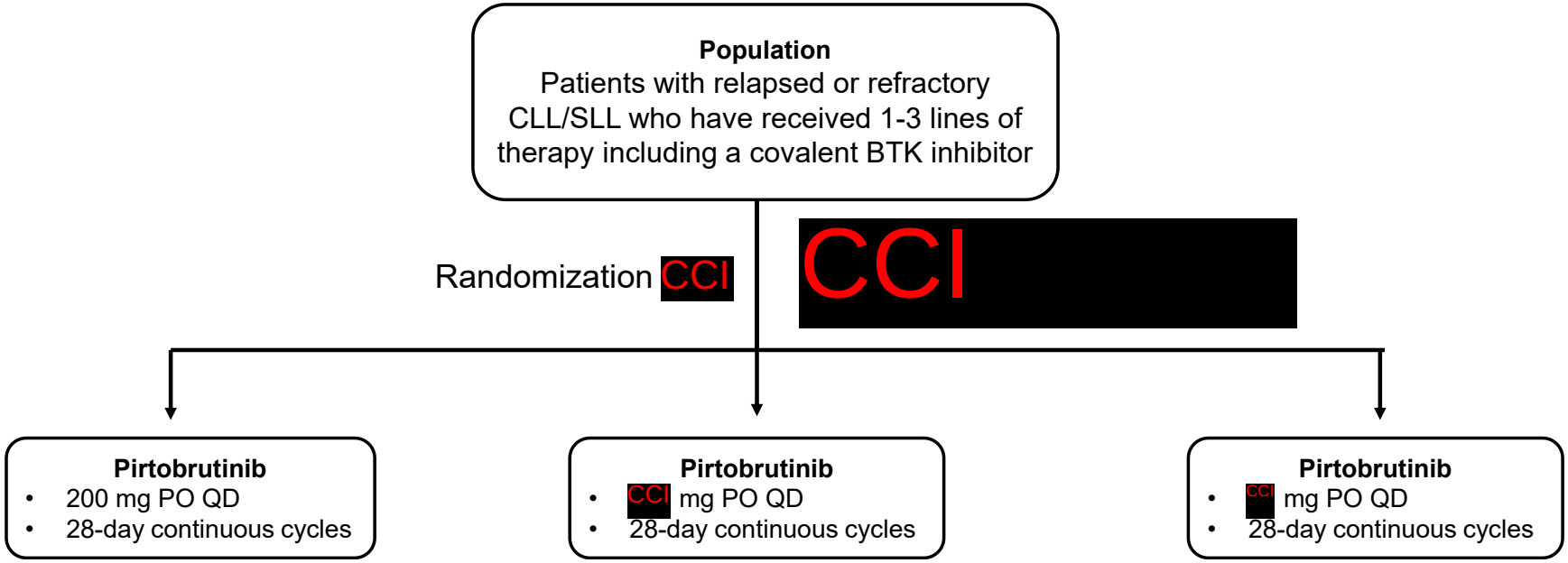
**Ethical Considerations of Benefit/Risk:**

The safety and effectiveness of pirtobrutinib treatment for participants with CLL/SLL support the overall benefit-risk of individuals taking part in this study.

**Data Monitoring Committee: No**

An assessment committee internal to Lilly will review safety and efficacy data during the study.

## 1.2. Schema




Abbreviations: BTK = Bruton tyrosine kinase; CLL/SLL = chronic lymphocytic leukemia/small lymphocytic lymphoma; CCI PO = oral; QD = once daily.

## 1.3. Schedule of Activities (SoA)

Every effort should be made to conduct all procedures within the same day. However, visit procedures may be conducted over more than 1 day if all activities are completed within the allowed visit tolerance period of each visit.

**Screening**

Please allow 7-10 business days from when a participant is entered in IWRS for screening to randomization.

Procedures conducted as part of the patient's routine clinical management and obtained before signing of the ICF may be used for screening or baseline purposes. CT/MRI may be considered valid if conducted within 42 days of planned randomization, with sponsor approval.

**C1D1**

The start of treatment at C1D1 should occur within 5 business days after randomization. A delay between randomization and C1D1 due to holiday, weekend, bad weather, or other unforeseen circumstances will be permitted for a maximum of 7 additional days with sponsor permission and proper documentation in the participant's medical record.

**Cycles**

Each cycle is 28 days long and is fixed and anchored to C1D1 independent of any dose holds.

**Posttreatment follow-up**

***Short-term follow-up***

Short-term follow-up (Visit 801) occurs 28 + 7 days after the participant and investigator agree that the participant will no longer continue study intervention. If the decision to permanently discontinue treatment occurs after the investigator temporarily withholds the study intervention, then the short-term follow-up visit can occur sooner, as long as at least 28 days have passed since the last dose of study intervention.

If a participant needs to start a new therapy that is not part of this study, and if medically appropriate, the participant should complete the short-term follow-up procedures before introduction of the new agent, even if the interval is less than 28 days from the last dose of study intervention.

***Long-term follow-up***

Long-term follow-up (Visit 802) begins when the participant completes the short-term follow-up visit and ends with either the end of study, withdrawal of consent, loss to follow-up, or the participant's death, whichever is earlier.

This visit may be conducted as a telehealth visit if no study procedures are scheduled.

***Discontinuation of study intervention***

For participants who discontinue treatment before documented disease progression, collect disease assessments, including hematology, physical examination, and imaging, until disease progression or the participant starts an alternative cancer therapy.

After discontinuation from study intervention, collect anticancer therapy information every 12 weeks from the end of the short-term follow-up for the first 2 years, and approximately every 24 weeks thereafter until death, withdrawal by the participant, lost to follow-up, or end of study.

### 1.3.1. Schedule of Activities

| **Study JZNX** | **Screening** | **Study Treatment Cycle = 28 days** | | | **Posttreatment** | | **Instructions** |
|---|---|---|---|---|---|---|---|
| **Cycle/Visit** | **Baseline (Day Relative to C1D1)** | **Cycles 1-6** | **Cycles 7-24** | **Cycles 25+** | **Short-Term Follow-Up (STFU)** | **Long-Term Follow-Up†† (LTFU)** | **Cycles 1-6**: visits occur at each cycle.<br>**Cycles 7-24**: visits occur Q16W at C9, C13, C17, C21, and C25.<br>**Cycles 25+:** visits occur Q24W.<br>†† Occurs every 16 weeks for first 2 years relative to C1D1, and then every 24 weeks. |
| **Day of cycle or visit** | | **Day 1** | **Day 1** | **Day 1** | **V801** | **V802-8XX** | |
| **Visit window (days)** | Up to 28 | ± 7 | ± 14 | ± 14 | 28 + 7 | ±14 | **C1D1:** see visit window instructions in Section 1.3. |
| Informed consent | X | | | | | | The ICF must be signed before any protocol-specified procedures are performed. |
| Preexisting conditions and medical history | X | | | | | | Collect all ongoing conditions and relevant past surgical and medical history. |
| Documentation of diagnosis and relevant biomarkers | X | | | | | | De-identified pathology report(s) confirming diagnosis of CLL/SLL may be requested.<br>Refer to Section 5. |
| Demographics | X | | | | | | |
| Concomitant medications | X | X | X | X | X | | **Cycles 1-6**: collect at each visit.<br>**Cycles 7-24**: collect at C9, C13, C17, C21, and C25.<br>**Cycles 25+:** collect Q24W.<br>**Discontinuation from study intervention:** see instructions in Section 1.3. |

| Study JZNX | Screening | Study Treatment Cycle = 28 days | | | Posttreatment | | Instructions |
|---|---|---|---|---|---|---|---|
| **Cycle/Visit** | **Baseline (Day Relative to C1D1)** | **Cycles 1-6** | **Cycles 7-24** | **Cycles 25+** | **Short-Term Follow-Up (STFU)** | **Long-Term Follow-Up†† (LTFU)** | **Cycles 1-6**: visits occur at each cycle.<br>**Cycles 7-24**: visits occur Q16W at C9, C13, C17, C21, and C25.<br>**Cycles 25+:** visits occur Q24W.<br>†† Occurs every 16 weeks for first 2 years relative to C1D1, and then every 24 weeks. |
| **Day of cycle or visit** | | **Day 1** | **Day 1** | **Day 1** | **V801** | **V802-8XX** | |
| **Visit window (days)** | Up to 28 | ± 7 | ± 14 | ± 14 | 28 + 7 | ±14 | **C1D1:** see visit window instructions in Section 1.3. |
| Adverse events (AEs) | X | X | X | X | X | X | Refer to Section 8.3.1 for timing of AE/SAE collection.<br>**Long-term follow-up:** only collect AEs and SAEs related to study treatment. Exceptions:<br>• If death due to AE occurs in LTFU and is not related to study treatment, record the AE that caused the death. Do not report the fatal event as an SAE.<br>• Collect information of all SPMs regardless of relatedness. |
| **Physical evaluation** | | | | | | | |
| Physical examination | X | X | X | X | X | X | Physical examination is a component of response assessment, along with hematology, and CT or MRI. Examinations occur at intervals relative to C1D1, regardless of any treatment interruptions.<br>**Cycles 1-24:** conduct at C1D1 and then Q16W from C1D1. Q16W corresponds to C5, C9, C13, C17, C21, and C25.<br>**Cycles 25+:** conduct Q24W.<br>**Long-term follow-up:** conduct only for participants who have not progressed or started another anticancer treatment. |
| Symptom-directed physical assessment | | X | | | | | At the discretion of the investigator or qualified personnel per local regulations, as indicated based on participant status and standard of care. Qualified personnel per local regulations will perform the assessment. |
| ECOG PS | X | X | X | X | X | | **Cycles 1-6:** conduct at each visit.<br>**Cycles 7-24:** conduct at C9, C13, C17, C21, and C25.<br>**Cycles 25+:** conduct Q24W. |
| Vital signs | X | X | X | X | X | | **Cycles 1-6:** conduct at each visit.<br>**Cycles 7-24:** conduct at C9, C13, C17, C21, and C25.<br>**Cycles 25+:** conduct Q24W. |
| 12-lead ECG (single) | X | X | X | X | X | | **C1D1:** Predose ECG.<br>**Cycles 1-6:** conduct at each visit. |

| Study JZNX | Screening | Study Treatment Cycle = 28 days | | | Posttreatment | | Instructions |
|---|---|---|---|---|---|---|---|
| **Cycle/Visit** | **Baseline (Day Relative to C1D1)** | **Cycles 1-6** | **Cycles 7-24** | **Cycles 25+** | **Short-Term Follow-Up (STFU)** | **Long-Term Follow-Up†† (LTFU)** | **Cycles 1-6**: visits occur at each cycle.<br>**Cycles 7-24**: visits occur Q16W at C9, C13, C17, C21, and C25.<br>**Cycles 25+:** visits occur Q24W.<br>†† Occurs every 16 weeks for first 2 years relative to C1D1, and then every 24 weeks. |
| **Day of cycle or visit** | | **Day 1** | **Day 1** | **Day 1** | **V801** | **V802-8XX** | |
| **Visit window (days)** | Up to 28 | ± 7 | ± 14 | ± 14 | 28 + 7 | ±14 | **C1D1:** see visit window instructions in Section 1.3. |
| | | | | | | | **Cycles 7-24:** conduct at C9, C13, C17, C21, and C25.<br>**Cycles 25+:** conduct Q24W.<br>Refer to Section 8.2.3. |
| **Disease assessments** | | | | | | | |
| CT or MRI | X | X | | X | X | X | **Screening:** CT or MRI may be considered valid if conducted within 42 days of planned randomization, with sponsor approval.<br>**Cycles 1-24:** conduct during screening and then Q16W from C1D1. Q16W corresponds to C5, C9, C13, C17, C21, and C25.<br>**Cycles 25+:** conduct Q24W.<br>Perform in between visits if disease progression is suspected. Imaging not needed after documented disease progression.<br>**Short-term follow-up:** Collect images if participant discontinues treatment and previous images were collected >6 weeks ago. Imaging not needed after documented disease progression.<br>**Long-term follow-up:** Conduct only for participants who have not progressed or started another anticancer treatment.<br>**Discontinuation from study intervention:** see instructions in Section 1.3. |

| Study JZNX | Screening | Study Treatment Cycle = 28 days | | | Posttreatment | | Instructions |
|---|---|---|---|---|---|---|---|
| **Cycle/Visit** | **Baseline (Day Relative to C1D1)** | **Cycles 1-6** | **Cycles 7-24** | **Cycles 25+** | **Short-Term Follow-Up (STFU)** | **Long-Term Follow-Up†† (LTFU)** | **Cycles 1-6**: visits occur at each cycle.<br>**Cycles 7-24**: visits occur Q16W at C9, C13, C17, C21, and C25.<br>**Cycles 25+:** visits occur Q24W.<br>†† Occurs every 16 weeks for first 2 years relative to C1D1, and then every 24 weeks. |
| **Day of cycle or visit** | | **Day 1** | **Day 1** | **Day 1** | **V801** | **V802-8XX** | |
| **Visit window (days)** | Up to 28 | ± 7 | ± 14 | ± 14 | 28 + 7 | ±14 | **C1D1:** see visit window instructions in Section 1.3. |
| **Laboratory tests and sample collection** | | | | | | | |
| Hematology | X | X | X | X | X | X | Hematology is a component of response assessment, along with physical examination, and CT or MRI.<br>Hematology occurs at intervals relative to C1D1, regardless of any treatment interruptions.<br>**C1D1:** Screening results within 3 days of C1D1 are acceptable as C1D1 results.<br>**Cycles 1-6:** conduct at each visit.<br>**Cycles 7-24:** conduct at C9, C13, C17, C21, and C25.<br>**Cycles 25+:** conduct Q24W.<br>**Long-term follow-up:** Conduct only for participants who have not progressed or started another anticancer treatment. |
| Clinical chemistry | X | X | X | X | X | | **C1D1:** Screening results within 3 days of C1D1 are acceptable as C1D1 results.<br>**Cycles 1-6:** conduct at each visit.<br>**Cycles 7-24:** conduct at C9, C13, C17, C21, and C25.<br>**Cycles 25+:** conduct Q24W.<br>Lactate dehydrogenase, calcium, magnesium, phosphorus, and uric acid (urate) are only required at Screening and Day 1 of C1 to C4. |
| Urine chemistry | X | X | | | | | **After screening:** As clinically indicated. |
| HCV | X | | | | | | If HCV antibody test is positive, it must be followed by an HCV RNA test. See Section 5.2. |
| HBV | X | X | | | | | See Sections 5.2 and 8.2.7 for details. |
| CMV PCR | X | | | | | | |
| Immunoglobulin panel | X | | | | | | |
| Coagulation panel | X | X | | | | | **After screening:** As clinically indicated. |

| Study JZNX | Screening | Study Treatment Cycle = 28 days | | | Posttreatment | | Instructions |
|---|---|---|---|---|---|---|---|
| **Cycle/Visit** | **Baseline (Day Relative to C1D1)** | **Cycles 1-6** | **Cycles 7-24** | **Cycles 25+** | **Short-Term Follow-Up (STFU)** | **Long-Term Follow-Up†† (LTFU)** | **Cycles 1-6**: visits occur at each cycle.<br>**Cycles 7-24**: visits occur Q16W at C9, C13, C17, C21, and C25.<br>**Cycles 25+:** visits occur Q24W.<br>†† Occurs every 16 weeks for first 2 years relative to C1D1, and then every 24 weeks. |
| **Day of cycle or visit** | | **Day 1** | **Day 1** | **Day 1** | **V801** | **V802-8XX** | |
| **Visit window (days)** | Up to 28 | ± 7 | ± 14 | ± 14 | 28 + 7 | ±14 | **C1D1:** see visit window instructions in Section 1.3. |
| Pregnancy test (serum or urine) | X | X | | | X | | Collect for individuals of childbearing potential. See Section 10.4 for definitions.<br>**Screening:** Serum sample preferred.<br>**C1D1:** Perform within 24 hr before the first dose of pirtobrutinib.<br>**At any time during the study:** monthly or as required per local regulations or institutional guidelines.<br>**STFU:** Serum sample preferred. |
| Bone marrow biopsy | | X | | | | | Only collect and evaluate locally to confirm CR or disease progression due to cytopenia.<br>See Section 8.1.3. |
| CCI | | | | | | | |
| **Stored samples** | | | | | | | |
| CCI | | | | | | | |
| **Randomization, dosing, dosing diary, and IWRS** | | | | | | | |
| Register visit with IWRS | X | X | X | X | X | | Visits are C1-6, C9, C13, C17, C21, C25, and then Q24W. |
| Randomization via IWRS | X | | | | | | Upon confirmation of eligibility. |
| Dispense pirtobrutinib | | X | X | X | | | Dosing is oral daily (continuous). |
| Dispense participant dosing diary | | X | | | | | |

| Study JZNX | Screening | Study Treatment Cycle = 28 days | | | Posttreatment | | Instructions |
|---|---|---|---|---|---|---|---|
| **Cycle/Visit** | **Baseline (Day Relative to C1D1)** | **Cycles 1-6** | **Cycles 7-24** | **Cycles 25+** | **Short-Term Follow-Up (STFU)** | **Long-Term Follow-Up†† (LTFU)** | **Cycles 1-6**: visits occur at each cycle.<br>**Cycles 7-24**: visits occur Q16W at C9, C13, C17, C21, and C25.<br>**Cycles 25+:** visits occur Q24W.<br>†† Occurs every 16 weeks for first 2 years relative to C1D1, and then every 24 weeks. |
| **Day of cycle or visit** | | **Day 1** | **Day 1** | **Day 1** | **V801** | **V802-8XX** | |
| **Visit window (days)** | Up to 28 | ± 7 | ± 14 | ± 14 | 28 + 7 | ±14 | **C1D1:** see visit window instructions in Section 1.3. |
| Participant returns dosing diary for site review | | X | | | | | |
| Assess dosing compliance | | X | X | X | | | |
| **Participant status** | | | | | | | |
| Survival status | X | | | | | | |

Abbreviations: C = cycle; C1D1 = Cycle 1 Day 1; CLL = chronic lymphocytic leukemia; CMV PCR = cytomegalovirus polymerase chain reaction; CR = complete remission; CT = computed tomography; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group Performance Status; FISH = fluorescence in situ hybridization; HBV = hepatitis B virus; HCV = hepatitis C virus; ICF = informed consent form; IWRS = interactive web-response system; MRI = magnetic resonance imaging; Q16W = every 16 weeks; Q24W = every 24 weeks; SAE = serious adverse event; SLL = small lymphocytic lymphoma; SPM = second primary malignancy.

### 1.3.2. Schedules for Pharmacokinetic Sampling

See Section 8.4 for details.

Sampling schedule A will be used to collect PK blood samples for CCI participants in each dose group (200 mg, CCI ).

| Study JZNX PK Sampling Schedule A | Study Treatment | Instructions |
|---|---|---|
| CCI | | |

Sampling schedule B will be used to collect PK blood samples for the remaining CCI participants in each dose group (200 mg, CCI CCI

| Study JZNX PK Sampling Schedule B | Study Treatment | Instructions |
|---|---|---|
| CCI | | |

# 2. Introduction

## CLL/SLL and current treatments

CLL/SLL is the most common form of adult leukemias in the Western world and accounts for approximately 30 to 40% of all leukemias (Goldin and Slager 2007; Eichhorst et al. 2015; Wierda et al. 2020). The treatment landscape for patients with CLL/SLL has changed radically over the last 10 years, resulting in markedly improved long-term outcomes (Burger 2020).

While chemoimmunotherapy had previously formed the foundation of therapy, more recent insights into the biological dependence of CLL/SLL on B-cell receptor signaling as well as antiapoptotic machinery have led to the successful development of several novel targeted therapies, including agents inhibiting BTK, BCL2, and PI3K-δ. The introduction of these novel agents, particularly the covalent BTK inhibitors, such as ibrutinib, acalabrutinib, and zanubrutinib, and the BCL2 inhibitor venetoclax, has substantially improved the outcome of patients with CLL and has become the main treatment for both patients with treatment-naïve and relapsed disease (Burger et al. 2015; Fischer et al. 2019; Shanafelt et al. 2019; Woyach et al. 2019).

Although irreversible BTK inhibitors have transformed the treatment of several B-cell malignancies, their long-term efficacy is ultimately limited by acquired resistance and toxicity, and despite available therapies, CLL/SLL remains an incurable disease.

## Pirtobrutinib

Pirtobrutinib is a novel oral, highly potent, selective, reversible BTK inhibitor with pharmacological properties that enable sustained inhibition throughout the once-daily dosing interval, regardless of intrinsic BTK turnover rate or prior BTK inhibitor treatment (Brandhuber et al. 2018; Mato et al. 2021). Pirtobrutinib is distinct from the covalent BTK inhibitors on the basis of its selectivity, favorable pharmacologic and pharmacokinetic properties, and noncovalent binding mode (Brandhuber et al. 2018).

Pirtobrutinib is active in patients with heavily pretreated CLL/SLL, including in patients who have received previous BTK inhibitors (Brandhuber et al. 2018; Mato et al. 2021). Clinical activity of pirtobrutinib has also been demonstrated in patients with known and unknown resistance mechanisms to previous BTK inhibitors, as well as in patients who discontinued a previous BTK inhibitor due to intolerance (Mato et al. 2021). Consistent with its high selectivity, pirtobrutinib was safe and well-tolerated in patients, including those previously treated with a BTK inhibitor.

The FDA granted accelerated approval to pirtobrutinib 200 mg QD for adults with CLL/SLL who have received at least 2 prior lines of therapy, including a BTK inhibitor and a BCL2 inhibitor. FDA also granted accelerated approval to pirtobrutinib 200 mg QD for adults with MCL after at least 2 lines of systemic therapy, including a BTK inhibitor.

Detailed information about pirtobrutinib, including nonclinical and clinical results, may be found in the prescribing information (Jaypirca package insert, 2023) and the IB.

## 2.1. Study Rationale

This study is a post-marketing requirement (PMR 4557-2) to the FDA to further assess the efficacy and safety of 3 dose levels of pirtobrutinib in patients with relapsed or refractory CLL or SLL, who have received 1-3 lines of treatment including a covalent BTK inhibitor.

Although different dose levels were evaluated in the LOXO-BTK-18001 study, relatively few participants were treated at doses lower than 200 mg, thus the need to further explore if a reduced dose could improve the safety profile without compromising efficacy.

## 2.2. Background

Pirtobrutinib 200 mg QD is currently under clinical development for the treatment of CLL/SLL and B-cell non-Hodgkin lymphoma, with 4 ongoing Phase 3 studies enrolling approximately 1500 participants with CLL/SLL. The FDA-accelerated approval for adults with CLL/SLL was based on Study LOXO-BTK-18001 (BRUIN), hereafter referred to as Study 18001.

**Study LOXO-BTK-18001**

Study 18001 is a Phase 1/2, open-label, international, single-arm, multicohort study of pirtobrutinib as monotherapy and as part of combination therapy in patients with CLL/SLL and non-Hodgkin lymphoma who failed or were intolerant to standard of care. The information provided from this study is based on a data cutoff in February 2023.

This study included monotherapy and combination treatment parts, evaluating 7 dose levels within the dose range of 25 mg to 300 mg QD.

***Pharmacokinetics***

Pirtobrutinib exhibited linear dose-proportional exposures over the entire dosing range of 25 mg to 300 mg QD.

***Efficacy***

Efficacy was observed at all dose levels and established based on overall response rate and duration of response by IRC assessment.

This table describes the results in participants with CLL/SLL who were previously treated with a BTK inhibitor and received pirtobrutinib at a starting dose of 200 mg QD without subsequent dose escalation (N = CCI).

| **Study 18001** | **Based on IRC review** |
|---|---|
| **Best overall response (n [%])** | CCI |
| CR | |
| CRi | |
| nPR | |
| PR | |
| PR-L | |
| Stable Disease | |
| PD | |
| **Overall response rate** | |
| (n [%]) | |
| 95% CI | |

| Study 18001 | Based on IRC review |
|---|---|
| **Duration of Response in months** | CCI |
| median | |
| 95% CI | |
| min, max | |
| **Overall response status (n [%])** | |
| Disease progression | |
| Died – no disease progression beforehand | |
| Censored | |

Abbreviations: CI = confidence interval; CR = complete remission; CRi = complete remission with incomplete hematologic recovery; IRC = Independent Review Committee; PD = disease progression; nPR = nodular partial response; PR = partial response; PR-L = partial response with lymphocytosis.

***Safety***

As of February 2023, a total of CCI study participants received pirtobrutinib regardless of dose treated for CLL, MCL, and other NHL in the pivotal Phase 1/2 study 18001. Safety results showed a safe and manageable profile across all doses tested, no dose-limiting toxicities, and no identified maximum tolerated dose. The AE profile for pirtobrutinib is favorable and consistent with the known side effects with the BTK inhibitor class and characteristics of the disease. This is further described in Section 2.3.1.

## 2.3. Benefit/Risk Assessment

Detailed information about the known and expected benefits and risks and reasonably expected AEs of pirtobrutinib may be found in the IB and prescribing information.

### 2.3.1. Risk Assessment

**Potential risks for this study**

Overall, data from Study 18001 show that pirtobrutinib is well-tolerated and demonstrates a manageable safety profile. Risks in the proposed study populations are not expected to be less favorable given this trial will include populations already studied within Study 18001, or in earlier lines of treatment. The lower dose is also not expected to pose a higher safety risk given overall expected lower exposures.

***Pirtobrutinib safety***

Based on results from Study 18001, pirtobrutinib is safe and well-tolerated in patients who were previously treated with a BTK inhibitor, and patients who received multiple prior lines of therapy for CLL/SLL. The AE profile for pirtobrutinib is consistent with the known side effects of the BTK inhibitor class and characteristics of the disease.

The safety analysis results shown here are from participants with CLL/SLL who were previously treated with a BTK inhibitor and received pirtobrutinib at a starting dose of 200 mg QD without subsequent dose escalation (N = CCI). The median duration of treatment was CCI months (range CCI). This table summarizes the occurrence of AEs in participants.

| Study 18001 | |
|---|---|
| **AE Category** | **Number of participants (%)** |
| **Any AE** | CCI |
| All | |
| Related to pirtobrutinib | |
| **Grade 3 or 4 AE** | |
| All | |
| Related to pirtobrutinib | |
| **AE leading to treatment discontinuation** | |
| All | |
| Related to pirtobrutinib | |
| **AE leading to dose reduction** | |
| All | |
| Related to pirtobrutinib | |
| **AE leading to treatment interruption** | |
| All | |
| Related to pirtobrutinib | |
| **SAE** | |
| All | |
| Related to pirtobrutinib | |
| **Fatal AE** | |
| All | |
| Related to pirtobrutinib | |

This table describes the most common AEs reported.

| Study 18001 | Maximum severity n (%) | | | | | |
|---|---|---|---|---|---|---|
| **AE preferred term** | **Grade 1** | **Grade 2** | **Grade 3** | **Grade 4** | **Grade 5** | **Total** |
| Fatigue | CCI | | | | | |
| Diarrhea | | | | | | |
| COVID-19 | | | | | | |
| Contusion | | | | | | |
| Cough | | | | | | |
| Neutrophil count decreased | | | | | | |

This table describes AEs of special interest.

| Study 18001 | Number of participants (%) | | |
|---|---|---|---|
| **AE composite term** | **Any Grade** | **Grade 3 or 4** | **Grade 5** |
| Infection including COVID-19 | CCI | | |
| Infection excluding COVID-19 | | | |
| Bleeding | | | |
| Neutropenia | | | |
| Thrombocytopenia | | | |
| Atrial fibrillation/flutter | | | |

In addition to the data from the open-label Study 18001, no specific safety concerns were raised by the respective independent data-monitoring committees reviewing the unblinded aggregated safety data from more than 600 pirtobrutinib-treated participants enrolled across 4 ongoing

Phase 3 pirtobrutinib studies in CLL/SLL participants. The Phase 3 studies include participants who receive pirtobrutinib as first-line treatment and pretreated participants. No new safety concerns were identified through regular sponsor medical review of individual AEs.

*Pirtobrutinib safety and exposure across a range of dose levels*

The safety profile with 200 mg QD is well established and is currently approved in the United States for adults with CLL/SLL, who have received at least 2 prior lines of therapy, including a BTK inhibitor and a BCL2 inhibitor.

Although there are limited data for lower dose levels, safety data and exposure-response analyses from 25 mg QD to 300 mg QD suggest there is no clear evidence of increased risk with higher exposures across the range of exposures for the CLL/SLL population, including for the 7 safety endpoints:

- Grade ≥ 3 anemia
- Grade ≥ 3 neutropenia
- Grade ≥ 3 thrombocytopenia
- Grade ≥ 3 infection/infestation
- any grade hypertension
- any grade bleeding, and
- any Grade ≥ 3 event.

The wide range of exposures were well-tolerated.

**Management of risks**

This clinical protocol is designed to mitigate risks to participants through a detailed plan for safety monitoring, systematic review of AEs, SAEs, dose modification for AEs, and an active pharmacovigilance review to assess for safety signals or trends. The study design ensures that all participants receive appropriate monitoring and standard-of-care treatment designed to mitigate risks to the participant (see Sections 1.3, 8.2, and 8.3).

### 2.3.2. Benefit Assessment

Despite available therapies, CLL/SLL remains an incurable disease. The efficacy of pirtobrutinib treatment at 200 mg QD was evaluated in Study 18001 based on the overall response rate and duration of response in participants with relapsed CLL/SLL, who had received prior BTK inhibitor (see Section 2.2).

Although the magnitude of benefit to participants randomized to the lower dose levels is unknown, it is reasonable to expect that they will experience a meaningful benefit based on the limited data to date.

The potential benefit from participation in this study also includes improvement of clinical outcomes and expert medical care for the study duration.

### 2.3.3. Overall Benefit-Risk Conclusion

The safety and efficacy profile seen to date for pirtobrutinib supports the overall favorable benefit-risk for participants with CLL/SLL in this study.

# 3. Objectives, Endpoints, and Estimands

| Objectives | Endpoints |
|---|---|
| **Primary** | |
| To compare the overall response rate of<br>• pirtobrutinib 200 mg to CCI, and<br>• pirtobrutinib 200 mg to CCI | Overall response rate, as assessed by the investigator per iwCLL 2018<br>Overall response rate is defined as the proportion of participants who achieve the best overall response at or before the initiation of subsequent anticancer therapy of<br>• CR<br>• CRi<br>• nPR, or<br>• PR |
| **Secondary** | |
| To determine the incidence of ≥Grade 3 AESIs that occur at each pirtobrutinib dose level | ≥Grade 3 AESIs (Section 8.3.3) |
| To determine the duration of response of each pirtobrutinib dose level | Duration of response<br>Duration of response is defined as the time from the date of the first documented CR, CRi, nPR, or PR to disease progression (per iwCLL 2018) or death from any cause |
| To determine the safety and tolerability of each pirtobrutinib dose level | Including, but not limited to<br>• ≥Grade 3 TEAEs<br>• SAEs<br>• discontinuations due to an AE<br>• dose interruptions due to an AE, and<br>• dose reductions due to an AE |
| **Exploratory** | |
| To evaluate efficacy of each pirtobrutinib dose level | • Progression-free survival<br>• Overall survival<br>  ○ Overall response rate and duration of response, including |

| Objectives | Endpoints |
|---|---|
| | partial remission with lymphocytosis |
| To evaluate the relationship between biomarkers and clinical outcomes | • Biomarkers assessed from blood samples and clinical outcomes data |
| To measure changes in biomarkers in response to pirtobrutinib and after progression | • Changes in biomarkers in response to study treatment |
| To further characterize the pharmacokinetics of pirtobrutinib | • PK parameters including, but not limited to, Cmax, Tmax, and AUC |
| To determine the relationship between PK and drug effects, including efficacy and safety | • Relationship of PK parameters to drug effects (exposure-response relationships) |

Abbreviations: AE = adverse event; AESI = adverse events of special interest; AUC = area under the time-concentration curve; Cmax = maximum concentration; CR = complete remission; CRi = complete remission with incomplete hematologic recovery; iwCLL = International Workshop on Chronic Lymphocytic Leukemia; nPR = nodular partial response; PK = pharmacokinetics; PR = partial response; SAE = serious adverse events; TEAE = treatment-emergent adverse events; Tmax = time of Cmax.

**Primary Estimand**

The primary research question is

> *What is the relative treatment effect as measured by ORR between pirtobrutinib 200 mg QD and pirtobrutinib* CCI *QD, respectively, in participants with relapsed or refractory CLL/SLL who previously received a covalent BTK inhibitor?*

The corresponding research hypothesis to be tested is that treatment effect of pirtobrutinib 200 mg QD is superior to pirtobrutinib CCI and pirtobrutinib CCI QD in ORR.

***Estimand attributes***

The estimand for the primary objective is described by the following attributes:

*Population*

CLL/SLL participants as defined by protocol eligibility criteria in Section 5.

The primary analysis will be conducted in the ITT population.

*Endpoint*

ORR as assessed by investigator per iwCLL 2018 criteria. ORR is defined as the proportion of participants who achieve the BOR of CR, CRi, nPR, or PR at or before the initiation of subsequent anticancer therapy.

The difference in ORR for each comparison with corresponding CCI CCI will be summarized.

*Treatment condition*

The randomized study intervention will be administered in 28-day cycles until meeting any protocol-defined reason for study intervention discontinuation. See Section 7.1.

*Intercurrent-event strategies*

Death, PD, or subsequent anticancer therapy for CLL/SLL is handled with treatment policy strategy.

A participant's BOR is the best response recorded from Cycle 1 Day 1 until database lock, PD, death, or start of subsequent anticancer treatment, whichever is the earliest. Responses recorded after initiation of subsequent anticancer therapy will not be considered for BOR.

Participants without postbaseline tumor assessment will be considered as non-responders.

Study intervention discontinuation is handled with treatment policy strategy.

*Population-level summary measure*

The difference in ORR between once daily pirtobrutinib 200 mg and CCI and the difference in ORR between once daily pirtobrutinib 200 mg and CCI will be estimated.

***Rationale for estimand***

The interest lies in the relative treatment effect measured by difference in ORR. Response after subsequent anticancer therapy will not be considered, as subsequent anticancer therapy will confound the treatment effect of interest. Study intervention discontinuation is handled with treatment policy as it reflects clinical practice.

# 4. Study Design

## 4.1. Overall Design

This is a Phase 2, open-label, randomized study evaluating the efficacy and safety of different dose levels of pirtobrutinib in participants with relapsed or refractory CLL/SLL, who have received 1-3 lines of treatment, including a covalent BTK inhibitor.

This study will further evaluate the safety, tolerability, and efficacy of 3 different dosages of pirtobrutinib, 200 mg, CCI once daily.

The start of treatment at C1D1 should occur within 5 business days after randomization. With sponsor permission, a maximum of 7 additional days delay between randomization and C1D1 may occur due to holiday, weekend, bad weather, or other unforeseen circumstances. If this occurs, site staff should document the reason in the participant's medical record.

Participants will receive pirtobrutinib continuously in this study until discontinuation criteria are met (Section 7) or criteria are met for the end of study (Section 4.4).

**Posttreatment follow-up**

Short-term follow-up begins when the participant and investigator agree that the participant will no longer continue study intervention.

Long-term follow-up begins when the participant completes the short-term follow-up visit and ends with either the end of study, withdrawal of consent, loss to follow-up, or the participant's death, whichever is earlier.

See Section 1.3 for more information.

## 4.2. Scientific Rationale for Study Design

**Overall design**

Randomization will reduce bias in this comparative study.

CCI are considered appropriate for this population (Hallek et al. 2018).

See Section 4.3 for the justification for the 3 dose levels.

See Section 9.5 for the justification for sample size.

**Primary endpoint**

The defined overall response rate is considered appropriate to evaluate the efficacy of pirtobrutinib in participants with refractory or relapsed CLL/SLL and participants who received prior lines of treatment, including a BTK inhibitor.

ORR will offer an assessment of antitumor effect based on objective and standardized iwCLL criteria and will be compared between dose levels.

**Collection of demographic information**

In this study, collection of demographic information includes race and ethnicity. The scientific rationale is based on the need to assess variable response in safety and/or efficacy based on race or ethnicity. This question can be answered only if all the relevant data are collected.

## 4.3. Justification for Dose

The dose levels planned for this study were selected based on the totality of PK, safety, and efficacy data from the Study 18001. See Section 2.2 for efficacy results and Sections 2.2 and 2.3 for safety results.

Three dose levels were selected to compare the currently approved 200-mg dose to 2 lower dose levels. Based on the available data, the proposed doses for this study are 200 mg, CCI CCI

The chosen dose levels are anticipated to provide an exposure range that is pharmacologically active and provide an opportunity to observe any meaningful differences in efficacy or safety.

An assessment of the exposure (PK)-response relationships for safety and efficacy indicated a wide therapeutic window of concentrations for pirtobrutinib supporting the proposed dose levels of 200 mg, CCI

Safety results showed a safe and tolerable profile across all doses tested, with no dose-limiting toxicities, and no maximum tolerated dose was identified.

**Data supporting 200 mg QD dose**

The 200-mg dose is approved for use by the FDA for patients with CLL/SLL, who have received at least 2 prior lines of therapy, including a BTK inhibitor and a BCL2 inhibitor. This dose level was based on a well-tolerated safety profile, PK analyses consistent with a compelling level of target engagement as predicted by nonclinical models, and promising and durable antitumor activity.

At the 200-mg dose, CCI of participants are predicted to exceed 90% inhibition of BTK at steady state based on population PK simulation.

For the CLL/SLL populations previously treated with BTK inhibitors, the overall response rate to a starting dose of 200 mg QD is CCI based on IRC assessments.

**Data supporting CCI QD doses**

CLL/SLL populations previously treated with BTK inhibitors achieved a response rate of CCI based on IRC assessments in participants with a starting dose of 25 mg QD to 100 mg QD CCI CCI

Approximately CCI of participants at the CCI dose and approximately CCI of participants at the CCI are predicted to exceed 90% inhibition of BTK at steady state based on population PK simulation.

**Dose proportionality**

Pirtobrutinib exposure increases proportionally following QD doses ranging from 25 mg to 300 mg. When compared to 200 mg QD, the CCI doses are expected to result in a CCI and CCI mean exposure (AUC and Cmax) reduction, respectively, and may still maintain sufficient benefit as a treatment for CLL/SLL patients. These dose levels will allow differentiation of exposure across the proposed dose levels.

## 4.4. End of Study Definition

The final analysis of the primary endpoint will occur after all randomized participants have the opportunity to be followed for at least 12 months or approximately 36 months from the date the first participant is randomized, whichever occurs earlier.

Study completion and end of study will occur once data are available for the final analysis of the primary endpoint. Investigators will continue to follow the SoA for all participants until notified by Lilly that study completion has occurred.

# 5. Study Population

Participant eligibility for enrollment in the study is based on the criteria listed in this section. The inclusion and exclusion criteria used to determine eligibility should only apply at screening or other specified visits, and not continuously throughout the study.

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

## 5.1. Inclusion Criteria

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

**Age**

1. Participants must be 18 years of age or older, or of legal age per local regulations at the time of signing the informed consent.

**Type of patient and disease characteristics**

2. Have confirmed diagnosis of CLL/SLL, as defined by these iwCLL 2018 criteria
    a. lymphocytes expressing the surface antigen CD5 together with CD23 and at least 1 B-cell antigen, for example, CD19 and CD20, with either kappa or lambda light chain restriction. Cases with abnormal B cells expressing surface antigen CD5 together with surface CD23, but with undetectable light-chain expression, or with dim-to-negative kappa or lambda restricted expression, may also be included. Other atypical cases may be considered for inclusion with sponsor approval.
    b. $\geq 5 \times 10^9$ B lymphocytes/L (5000/μL) in the peripheral blood.
    For SLL patients, $< 5 \times 10^9$ B lymphocytes/L (5000/μL) in the peripheral blood is allowed, and
    c. ≤55% of blood lymphocytes are prolymphocytes.
3. Have a requirement for therapy consistent with iwCLL 2018 criteria for initiation of therapy such that at least 1 of the following should be met:
    - evidence of progressive marrow failure as manifested by the development of, or worsening of, anemia, such as hemoglobin <10 g/dL, or thrombocytopenia, such as platelets $\leq 100 \times 10^9$/L
    - massive, that is, spleen edge ≥6 cm below the left costal margin, progressive, or symptomatic splenomegaly >13 cm
    - massive nodes, that is, ≥10 cm in longest diameter, progressive or symptomatic lymphadenopathy
    - progressive lymphocytosis with an increase of >50% over a 2-month period or lymphocyte doubling time <6 months.
    Exclude factors contributing to lymphocytosis other than CLL/SLL, for example, infections or steroid administration
    - autoimmune complications, including or thrombocytopenia poorly responsive to corticosteroids
    - symptomatic or functional extranodal involvement (skin, kidney, lung, spine), or
    - disease-related symptoms as defined by any

- unintentional weight loss ≥10% within the previous 6 months
- fevers ≥100.5°F or 38.0°C for 2 or more weeks without evidence of infection
- night sweats for ≥1 month without evidence of infection, or
- significant fatigue.

4. Have an ECOG score of 0 to 2.
5. Must have laboratory test results within the ranges described in this table. Results from the most recent laboratory tests prior to enrollment will be used for eligibility.

| Test | Result |
|---|---|
| **Hematology** | |
| Absolute neutrophil count | ≥0.75 × $10^9$/L, or<br>≥0.50 × $10^9$/L in patients with documented bone marrow involvement considered to impair hematopoiesis.<br>Granulocyte-colony stimulating factor (G-CSF) support is permitted in patients with documented bone marrow involvement. |
| Platelet count | ≥50 × $10^9$/L, or<br>≥30 × $10^9$/L in patients with documented bone marrow involvement considered to impair hematopoiesis.<br>Transfusion support is permitted in patients with bone marrow involvement.† |
| Hemoglobin level | ≥8 g/dL (≥80 g/L), or<br>≥6 g/dL in patients with documented bone marrow involvement considered to impair hematopoiesis.<br>Transfusion support is permitted in patients with bone marrow involvement.† |
| † Patients must be responsive to transfusion support if given for thrombocytopenia or anemia. Patients known to be refractory to transfusion support are not eligible. If the patient is cytopenic, there should be no evidence of myelodysplasia or hypoplastic bone marrow. | |
| **Hepatic** | |
| Total bilirubin | ≤1.5 × ULN, or<br>≤3 × ULN with documented liver involvement and/or evidence of Gilbert's disease. |
| ALT and AST | ≤3.0 × the ULN, or<br>≤5 × ULN with documented liver involvement. |
| **Renal** | |
| Creatinine clearance | ≥30 mL/min<br>Using Cockcroft/Gault formula:<br>$\frac{(140 - \text{age}) \times \text{body weight (kg)}}{\text{serum creatinine (mg/dL)} \times 72} \times 0.85$ (if female) |

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of normal.

6. CCI [redacted]

**Previous treatment**

7. Prior CLL/SLL treatment
   - have received at least 1, but not more than 3 lines of, treatment for CLL/SLL, and
   - have received a covalent BTK inhibitor.

8. Have had a washout period planned before randomization for these treatments
   - previous BTK inhibitor - 5 half-lives or 1 week, whichever is longer
   - targeted agents or cytotoxic chemotherapy - 5 half-lives or 2 weeks, whichever is longer
   - therapeutic antineoplastic monoclonal antibodies - 5 half-lives or 4 weeks, whichever is longer, and
   - palliative limited field radiation – 1 week.
9. Prior treatment-related AEs must have recovered to Grade ≤1, pretreatment baseline or are controlled with medications without meeting other exclusion criteria.
   Exceptions – AEs of alopecia or disease-related symptoms, such as fever, fatigue, night sweats or weight loss.

**Contraception**

10. Contraceptive use by participants should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. For the contraception requirements of this protocol, see Section 10.4.

**Other inclusions**

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

**Informed consent**

13. Willing and capable of giving signed informed consent as described in Section 10.1.3, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

## 5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria applies:

**Medical conditions**

14. Have known or suspected Richter's transformation to diffuse large B-cell lymphoma, prolymphocytic leukemia, or Hodgkin's lymphoma at any time before randomization.
15. Have known or suspected history of central nervous system involvement by CLL/SLL.
16. Previous or concurrent cancer distinct from CLL/SLL within 3 years before randomization. Exceptions may occur with documented sponsor approval. Examples include
    - nonmelanoma skin cancer or lentigo maligna melanoma
    - cervical carcinoma in situ
    - localized prostate cancer undergoing active surveillance, and
    - localized (for example, lymph node negative) breast cancer with no evidence of active disease present for more than 3 years. Individual may be receiving adjuvant hormonal therapy.

17. Have a history of ≥Grade 3 bleeding due to treatment with a BTK inhibitor.
18. Have major surgery planned within 4 weeks of planned first dose of study intervention.
19. Have ongoing drug-induced liver injury, primary biliary cirrhosis, or extrahepatic obstruction caused by cholelithiasis, or cirrhosis of the liver.
20. Have significant cardiovascular disease defined as any of the following:
    a. unstable angina or acute coronary syndrome within the past 2 months before randomization
    b. history of myocardial infarction within 3 months before randomization
    c. documented LVEF by any method of ≤40% within the 12 months before randomization
       Exception – individual has ≥2 subsequent measurements of any kind, separated by a minimum of 3 weeks, that documents LVEF recovery >40%
    d. ≥Grade 3 New York Heart Association functional classification system of heart failure, or
    e. uncontrolled or symptomatic arrhythmias.
21. Have a QTc prolongation using Fridericia's formula (QTcF) >470 ms. See Section 8.2.3 for details and potential corrections.
22. Have hepatitis B testing results at screening indicating active infection defined as positive for HBsAg or PCR positive for HBV DNA.
    Exception - Individuals with negative HBsAg and positive anti-HBc if HBV DNA is negative before randomization.
23. Have HCV defined as positive for anti-HCV antibodies.
    Exception - Individuals positive for anti-HCV antibodies and negative for HCV RNA before randomization.
24. Have known active CMV infection as determined through CMV PCR testing.
25. Have known HIV infection, regardless of CD4 count.
26. Have an unstable mental health disorder.
27. Have evidence of a clinically significant uncontrolled medical condition(s) including, but not limited to, hypertension, 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 participation.
    Screening for chronic conditions is not required.
28. Have a clinically significant active malabsorption syndrome or other condition likely to affect gastrointestinal absorption of the oral-administered study treatments.
29. Have inflammatory bowel disease.

**Previous or concomitant therapy**

30. Have received prior treatment with
    - a BTK degrader, or
    - a noncovalent BTK inhibitor.
31. Have a history of allogeneic transplant.
32. Have had an autologous stem cell transplant or chimeric antigen receptor T-cell therapy within the past 90 days.
33. Require therapeutic anticoagulation with warfarin or another vitamin K antagonist.
34. Use >20-mg prednisone QD or equivalent dose of steroid per day at the time of first dose of study intervention.
35. Received a live vaccine within 28 days before randomization.
36. Require therapy with a strong CYP3A inhibitor that cannot be stopped within 14 days before the first dose of study intervention. See Section 10.8 for examples of excluded medications and suggested alternatives that are not strong CYP3A inhibitors.
37. Require therapy with a strong or moderate CYP3A4 inducer that cannot be stopped within 14 days before the first dose of study intervention. See Section 10.8 for examples of excluded medications.
38. Require therapy with substrates of P-gp and BCRP that are sensitive to minimal concentration changes. See Section 10.8 for examples of excluded medications.
39. Are currently enrolled in any other clinical study involving an investigational product or anticancer therapy except hormonal therapy. Individuals receiving investigational COVID-19 prophylaxis or treatment may be allowed in the study with sponsor approval.

**Other exclusions**

40. Are pregnant, or intend to become pregnant during the study, or within 30 days of last dose of study treatment or to breastfeed during the study or within 1 week of the last dose of study treatment.
41. Have a known hypersensitivity, including anaphylaxis, to any component or excipient of pirtobrutinib.
42. Are special protected populations, including those unable to sign consent for themselves.
43. Are individuals committed to an institution by virtue of an order issued with by the judicial or administrative authorities.
44. Are employees of the sponsor or site.

## 5.3. Lifestyle Considerations

This section is not applicable to this study.

## 5.4. Screen Failures

A screen failure occurs when a participant who consents to participate in the clinical study is not subsequently randomized. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Each time rescreening is performed, the individual must sign a new ICF and will be assigned a new identification number.

Rescreened individuals must repeat screening procedures and tests, with the exception of imaging, if done within 42 days of planned randomization.

Repeating of laboratory tests during the screening period or repeating screening tests to comply with the protocol designated screening period does not reconstitute rescreening.

## 5.5. Criteria for Temporarily Delaying Enrollment of a Participant

This section is not applicable to this study. All entry criteria must be met within the specified intervals in the SoA.

See Section 10.7 for changes in study conduct during exceptional circumstances.

# 6. Study Intervention(s) and Concomitant Therapy

Study intervention is defined as any medicinal product(s) or medical device(s) intended to be administered to or used by a study participant according to the study protocol.

## 6.1. Study Intervention(s) Administered

This table lists the interventions used in this clinical study.

| **Intervention Name** | **Pirtobrutinib** |
|---|---|
| **Dosage Level(s)** | CCI [redacted] or 200 mg |
| **Dose Frequency** | Once daily (QD) in 28-day continuous cycles |
| **Route of Administration** | Oral |
| **Authorized as Defined by EU Clinical Trial Regulation** | Not authorized in EU |

**Pirtobrutinib**

The participant should take pirtobrutinib at approximately the same time each day.

Pirtobrutinib may be taken with food or drink.

A vomited dose should not be redosed or replaced.

If a dose is missed by more than 12 hours, then the participant should wait and take the next dose as scheduled.

**Packaging and labeling**

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

## 6.2. Preparation, Handling, Storage, and Accountability

The investigator or designee must confirm appropriate storage conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.

Only participants enrolled in the study may receive study intervention. Only authorized study personnel may supply, prepare, or administer study intervention.

All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized study personnel.

The investigator or authorized study personnel are responsible for study intervention accountability, reconciliation, and record maintenance, that is, receipt, reconciliation, and final disposition records.

Further guidance and information for the final disposition of unused study interventions are provided in the study training materials.

## 6.3. Assignment to Study Intervention

**Randomization** CCI

All participants will be centrally assigned to randomized study intervention using an IWRS. Before the study is initiated, the log-in information and directions for the IWRS will be provided to each site.

Study intervention will be dispensed at the study visits summarized in SoA.

Returned study intervention should not be re-dispensed to the participants.

Participants will be randomly assigned in a CCI ratio to receive either pirtobrutinib 200 mg, CCI

Participants will be CCI
CCI

## 6.4. Blinding

This is an open-label study.

## 6.5. Study Intervention Compliance

Participants must keep a daily diary to record dosing compliance of pirtobrutinib.

The site staff will assess dosing compliance at each visit by means of tablet count in returned bottles.

A record of the number of tablets dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays, or dose modifications, will also be recorded in the CRF and dosing diary.

Study intervention taken will be derived from the difference between the total number of tablets dispensed and returned over the course of the participant's treatment. A participant will be considered noncompliant if they are judged by the investigator to have intentionally or repeatedly taken <75% or ≥125% of the planned doses of study intervention over the course of the participant's treatment.

## 6.6. Dose Modification

Guidelines for making dose modifications in this study fall into these categories

- guidelines for adjusting study intervention
- guidelines for withholding study intervention
- guidelines for discontinuing study intervention
- guidelines for resuming a treatment cycle, and
- guidelines for re-escalating study intervention.

These recommendations serve as a guide and do not replace investigator judgment and applicable local recommendations if more stringent.

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

### 6.6.1. Guidelines for Adjusting or Withholding or Discontinuing Study Intervention to Manage AEs

The investigator may adjust the participant's dose or temporarily or permanently discontinue the participant from study intervention if the participant experiences a clinically significant AE as assessed by NCI CTCAE v5.0.

These principles guide investigators on when to adjust the 200-mg or CCI, or withhold, or discontinue the study intervention due to AEs.

Pirtobrutinib exhibits linear PK. The current guidance to manage AEs is to reduce the pirtobrutinib exposure level.

For participants receiving 200 mg QD, the reduction to 100 mg QD is equivalent to a 50% exposure reduction from the starting dose. A further reduction to 50 mg QD is equivalent to a 50% exposure reduction from 100 mg QD.

For participants receiving CCI QD, the reduction to CCI QD is equivalent to a CCI exposure reduction from the starting dose of CCI QD.

This table provides guidance to manage AEs.

| Adverse Events | Occurrences Requiring Dose Modification | Pirtobrutinib Dose Modification Instructions | | |
|---|---|---|---|---|
| | | 200 mg | CCI | |
| • Grade 3 or greater non-hematologic toxicity[a]<br>• Absolute neutrophil count <1 to 0.5 × $10^9$/L with fever and/or infection<br>• Absolute neutrophil count <0.5 × $10^9$/L lasting 7 or more days<br>• Platelet count <50 to 25 × $10^9$/L with bleeding<br>• Platelet count <25 × $10^9$/L | First occurrence | Hold pirtobrutinib until recovery to Grade 1 or baseline. May restart at original dose level.[b] | | |
| | Second occurrence | Hold pirtobrutinib until recovery to Grade 1 or baseline. May restart at 100 mg[c] | Hold pirtobrutinib until recovery to Grade 1 or baseline. May restart at CCI[c] | Discontinue |
| | Third occurrence | Hold pirtobrutinib until recovery to Grade 1 or baseline. May restart at 50 mg[c] | Discontinue | |
| | Fourth occurrence | Discontinue | | |

Dose modification is not recommended for asymptomatic lymphocytosis. Asymptomatic lipase increase may not necessarily warrant dose modification.

[a] Evaluate the benefit-risk before resuming treatment at the same dose for a Grade 4 non-hematological toxicity.

[b] If a Grade 3 or Grade 4 treatment-related AE takes longer than 21 days to recover to Grade 1 or baseline, reduce the dose after the first occurrence.

[c] If the dose was reduced previously for the same event, continue to the next lower dose level or discontinue.

The investigator should also refer to the IB for the current safety information.

**Additional guidelines for withholding study intervention**

If a participant needs surgery while on study intervention, the investigator should consider withholding study intervention for 3 to 7 days before and after surgery, depending on the type of surgery and risk of bleeding.

Investigators may withhold pirtobrutinib for a maximum of 28 days from the last dose to allow a participant sufficient time for recovery from treatment-related toxicity. In exceptional circumstances, a longer delay is permitted upon agreement between the investigator and the sponsor.

#### 6.6.1.1. Guidelines for Resuming a Treatment Cycle after Management of AE Toxicity

In the event of dosing interruptions due to toxicity, and subsequent restarting of pirtobrutinib, the cycle schedule and radiologic imaging schedule will not change.

Before resuming the next treatment cycle, AE toxicity must resolve to Grade ≤1 or baseline.

Exceptions include AEs with no immediate medical consequence that can be controlled with adequate treatment. Examples of such AEs include pain, alopecia, neuropathy, fatigue, nausea, vomiting, diarrhea, Grade 2 hypothyroidism, or Grade 2 hypertension.

### 6.6.2. Guidelines for Re-escalating Study Intervention

For participants who have undergone a dose reduction of pirtobrutinib, investigators may

- re-escalate their dose once the participant tolerates a reduced dose of pirtobrutinib for ≥2 weeks without toxicity, or
- maintain that dose, even if there is minimal or no toxicity with the reduced dose.

A re-escalation should not exceed the original starting dose.

If the AE that led to the dose reduction was not related to study intervention, the investigator may consider repeat re-escalations, not to exceed the starting dose, if tolerated.

## 6.7. Continued Access to Study Intervention after the End of the Study

Once criteria are met for the end of study, participants may have the opportunity to continue receiving pirtobrutinib in an open-label extension study or if pirtobrutinib is commercially available.

## 6.8. Treatment of Overdose

In the event of an overdose, the investigator or treating physician should

- contact the medical monitor immediately
- evaluate the participant to determine, in consultation with the medical monitor, whether study intervention should be interrupted or whether the dose should be reduced
- closely monitor the participant for any AE/SAE and laboratory abnormalities as medically appropriate until, for example, if a participant experiences an SAE because of a drug overdose the SAE should be reported immediately or within 24 hours from the knowledge of the event

- in the event that the overdose is associated with an SAE, the 2 events should be linked and the SAE reported as detailed in Section 10.3.5, and
- document the quantity of the excess dose and the duration of the overdose in the CRF.

For this study, an overdose is defined as any dosage that exceeds the maximum dosage in the protocol. There is no known antidote for overdose of pirtobrutinib. In the case of suspected overdose, monitor hematology, chemistry, and vital signs and provide supportive care as necessary and notify the sponsor.

## 6.9. Prior and Concomitant Therapy

**Concomitant therapy data collection**

For therapy that the participant is receiving at the time of enrollment or receives during the study, whether prescription or over-the-counter, authorized study personnel should collect

- the name of medication, vaccine, or therapy
- the reason for use
- route of administration, and
- dates of administration, including start and end dates.

Contact the medical monitor if there are any questions regarding concomitant or prior therapy.

### 6.9.1. Allowed Concomitant Therapy

**Anticancer medications**

Continuation of certain anticancer medications, such as hormonal therapy for participants with prior prostate cancer or breast cancer, is allowed. Examples of these anticancer medications include

- Gonadotropin-Releasing Hormone or Luteinizing Hormone-Releasing Hormone agonists
- aromatase inhibitors, or
- selective estrogen receptor modulators or degraders.

**Steroids**

Steroid use is allowed only in these conditions unless approved by the sponsor

- brief, limited use of systemic corticosteroids (≤7 days), where such use is considered standard of care, such as premedication for contrast allergy, short courses to treat asthma, and for chronic obstructive pulmonary disease
- chronic use of steroids (>7days) to treat symptoms from an immune-related AE
- systemic glucocorticoid use
    - to treat symptoms of an immune-related AE
    - for prevention of emesis
    - to premedicate for IV contrast allergies or reactions
    - as short-term oral or IV use in doses >10 mg/day prednisone equivalent to treat asthma or COPD exacerbations, and

    - as chronic systemic replacement doses, not to exceed 10 mg/day prednisone equivalent
- other glucocorticoid use
    - topical or ocular
    - intraarticular, and
    - inhalation for the management of asthma or COPD, and
- local steroid injections.

**Vaccines**

Killed vaccines are allowed.

Any licensed COVID-19 vaccine, including for Emergency Use, in a particular country is allowed if they are mRNA vaccines, adenoviral vaccines, or inactivated vaccines.

### 6.9.2. Prohibited Concomitant Therapy

Pirtobrutinib is a substrate of CYP3A. Concomitant medications that are strong inhibitors and strong or moderate inducers of CYP3A should be avoided as these agents may alter the exposure of pirtobrutinib. Pirtobrutinib is also a P-gp inhibitor, a moderate CYP2C8 and BCRP inhibitor, and a weak CYP2C19 and CYP3A inhibitor. Concomitant use of pirtobrutinib with sensitive P-gp, CYP2C8, BCRP, CYP2C19, or CYP3A substrates may increase their plasma concentrations, which may increase risk of AEs related to these substrates for drugs that are sensitive to minimal concentration changes.

Section 10.8 includes a table that summarizes potential drug-drug interaction risks and examples of commonly used oral medications in that drug class that should not be coadministered with pirtobrutinib during the study.

The following additional medications and vaccinations are prohibited during the study:

- any investigational product not specified in this protocol
- systemic anticancer agents not specified in this protocol
- herbal drugs known to have antitumor activity. Herbal agents are considered to have anticancer activity if they are included in local treatment guidelines or have randomized clinical data demonstrating benefit
- glucocorticoids except for use as noted in Section 6.9.1
- medications or vaccinations specifically prohibited in the exclusion criteria (Section 5.2)
- live or live attenuated vaccines within 30 days before the first dose of study intervention and 90 days after the last dose of study intervention, and
- investigational vaccines, that is, those not licensed or approved for Emergency Use, with the exception of COVID vaccines.

Medications or vaccinations specifically prohibited in the exclusion criteria (Section 5.2) are not allowed during the ongoing trial. If there is a clinical need for the participant to have any prohibited medication or vaccine, the investigator must consult with the sponsor's medical monitor.

Upon the observation of AEs following coadministration of pirtobrutinib with other medications, consult the product labels of pirtobrutinib and the concomitant drug(s) and consider adjusting dose or discontinuing the coadministered drug(s), as appropriate.

The final decision on any supportive therapy or vaccination rests with the investigator and/or the participant's treating physician.

### 6.9.3. Concomitant Therapy for Infections or Bleeding

See Section 8.2.7 for more information on monitoring for infections and bleeding.

**Infections**

The use of prophylactic antimicrobial therapy should be considered in all study participants when clinically appropriate. Local practices or guidelines regarding infection prophylaxis should be followed.

Prophylactic antibiotic or IV immunoglobulin therapy for management of participants at risk of infections may be considered. Initiation of prophylactic antibiotics against pneumocystis infection before study intervention administration may be warranted.

Examples of antimicrobial therapy include

- trimethoprim-sulfamethoxazole
- dapsone
- aerosolized pentamidine, and
- atovaquone.

**Bleeding**

The benefit versus risk of concurrent treatment with anticoagulation and antiplatelet therapy should be carefully considered for participants who require this therapy.

If a participant needs surgery, the benefit versus risk of withholding anticoagulation or antiplatelet therapy for at least 3 to days before and after surgery should be considered depending upon the type of surgery and the risk of bleeding.

The sponsor recommends withholding pirtobrutinib for at least 3 days before and after surgery where bleeding risk cannot be excluded.

### 6.9.4. Radiation Therapy

Local treatment while receiving study intervention, for example, palliative radiation therapy for symptomatic nodal disease, is permitted if the participant is not considered to be clinically or radiologically 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 participant may remain on study provided there is other evidence of disease that can be followed for determination of progression.

# 7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

Discontinuation of specific sites or of the study as a whole are handled as part of Section 10.1.

## 7.1. Discontinuation of Study Intervention

When necessary, a participant may be permanently discontinued from study intervention. If so, the participant will discontinue the study intervention (treatment) and will remain in the study to complete procedures for all remaining study visits, as shown in the SoA.

A participant should be permanently discontinued from study intervention if

- the participant or the participant's designee requests to discontinue study intervention
- the participant is noncompliant with study procedures or treatment
- there is disease progression determined by the investigator per iwCLL 2018 criteria. Sponsor verification of progressive disease may be requested
- the participant requires alternative treatment, unless the treatment is temporary, such as local radiation or surgery to relieve symptoms of the disease that does not otherwise meet the definition of disease progression
- there is a dose delay of more than 28 days for hematologic toxicity. In exceptional circumstances, a longer delay is permitted upon agreement between the investigator and the sponsor. See Section 10.7
- the participant becomes pregnant during the study, or
- in the opinion of the investigator, the participant should permanently discontinue the study intervention for safety reasons.

If the participant, for any reason, requires treatment from another therapeutic agent that is effective for the study indication, discontinuation from study intervention will occur prior to introduction of the new agent. If medically appropriate, complete the short-term follow-up procedures before introduction of the new agent; see Section 1.3.

If a participant has confirmed disease progression recorded and has discontinued study intervention, the participant will be followed up for survival status until death, withdrawal of consent for survival status, or the end of the study.

See Section 6.6 for additional guidelines for discontinuing study intervention.

### 7.1.1. Temporary Interruption of Study Intervention

See Section 6.6 for guidelines for withholding study intervention.

## 7.2. Participant Discontinuation/Withdrawal from the Study

Discontinuation is expected to be uncommon.

A participant may withdraw from the study

- at any time at the participant's own request for any reason or without providing any reason
- at the request of the participant's designee, for example, participant's legally authorized representative
- at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons
- if enrolled in any other clinical study involving an investigational product, or enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study, or
- if the participant dies.

If the participant has not already discontinued the study intervention, the participant will be permanently discontinued from the study intervention at the time of the decision to discontinue the study.

At the time of discontinuing from the study, if possible, the participant will complete procedures for a short-term follow-up visit, as shown in the SoA.

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, the participant may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

If a participant is considering withdrawing consent from the study and all further follow-up, the investigator should provide the participant with options for alternative follow-up methods, for example, discontinuation of follow-up clinical visits, but continued follow-up for survival. If the participant does not wish to be contacted for the necessary follow-up questions pertaining to survival, this should be clearly documented.

## 7.3. Lost to Follow-Up

A participant will be considered lost to follow-up if they repeatedly fail to return for scheduled visits and are unable to be contacted by the study site.

Site personnel or designee is expected to make diligent attempts to contact participants who fail to return for a scheduled visit or were otherwise unable to be followed up by the site.

Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomized, including those who did not get investigational product.

Public sources may be searched for vital status information. If vital status is determined to be deceased, this will be documented, and the participant will not be considered lost to follow-up.

# 8. Study Assessments and Procedures

Study procedures and their timing are summarized in the SoA Section 1.3.

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

## 8.1. Efficacy Assessments

### 8.1.1. Response Assessment

All participants must have clinical examination and response assessments during the course of treatment, while on study, and during follow-up as indicated in the SoA.

The investigator will conduct radiologic assessments locally and send images for central assessment according to the Imaging Manual.

The investigator will assess response using the iwCLL 2018 response criteria (Hallek et al. 2018), based on

- disease and symptom-focused physical examination
- imaging
- hematology results, and
- bone marrow examinations, as applicable.

See Section 8.1.4 for iwCLL response criteria guidance. Response assessments will include CR, CRi, nPR, PR, PR-L, SD, or PD (Cheson et al. 2012; Hallek et al. 2018).

**Disease progression**

Constitutional symptoms alone do not define PD. With approved BTK inhibitors, lymphocytosis and leukocytosis are well-documented on-target effects that occur early during treatment administration. These reactions are not reflective of PD in the absence of other signs of PD, for example, splenomegaly, enlarging lymph nodes, isolated new lymphocytosis, or disease-related constitutional symptoms and will not be considered PD.

Sponsor verification of progressive disease may be requested.

***Richter's transformation***

If Richter's transformation is suspected, the investigator should confirm the diagnosis using local standard of care procedures and document this in the EDC. If a PET-CT scan is performed, the results of this scan should be captured in the EDC.

### 8.1.2. Radiologic Imaging

To evaluate treatment response and recurrence, radiologic imaging is required until

- disease recurrence or progression
- the start of a new anticancer therapy
- death, or
- study completion.

Radiologic imaging may also be obtained as clinically indicated, which may be before the next scheduled scan.

Radiologic imaging timing should follow calendar days from randomization and should not be recalculated based on date of previous scans.

**Preferred method of imaging**

CT scan with IV contrast agent is the preferred method of assessment with scans of neck, chest, abdomen, and pelvis. However, MRI with contrast is acceptable if CT scan with contrast agent is contraindicated.

Use the same method of imaging throughout the study for each individual participant.

### 8.1.3. Bone Marrow Biopsy

Complete response assessment by the investigator should rely on local evaluation of the bone marrow.

### 8.1.4. iwCLL Response Criteria Guidance

| | Group A | | | | Group B | | |
|---|---|---|---|---|---|---|---|
| **Parameter** | **Lymph nodes** | **Liver or spleen size[a]** | **Constitutional symptoms** | **Circulating lymphocyte count** | **Platelet count** | **Hemoglobin** | **Marrow** |
| **CR** When all criteria are met. | None ≥1.5 cm | Spleen size <13 cm. Liver size normal | None | Normal[b] | ≥100 × $10^9$/L | ≥11.0 g/dL not transfused and without erythropoietin | Normo-cellular, no CLL cells, no B-lymphoid nodules |
| **PR[c]** When at least 2 of the criteria in Group A and 1 criterion in Group B improve after receiving study intervention. | Decrease ≥50% from baseline[d] | Decrease ≥50% from baseline | Any | Decrease ≥50% from baseline | ≥100 × $10^9$/L or increase ≥ 50% over baseline | ≥11.0 g/dL or increase ≥50% over baseline | Presence of CLL cells, or B-lymphoid nodules, or test not done |

| | Group A | | | | Group B | | |
|---|---|---|---|---|---|---|---|
| **Parameter** | **Lymph nodes** | **Liver or spleen size[a]** | **Constitutional symptoms** | **Circulating lymphocyte count** | **Platelet count** | **Hemoglobin** | **Marrow** |
| **PD[e]** When at least 1 criterion is met. | Increase ≥50% from nadir[f] | Increase ≥50% from nadir | Any | Increase ≥50% over nadir | Decrease of ≥50% from baseline secondary to CLL | Decrease of ≥2 g/dL from baseline secondary to CLL | Increase of CLL cells by ≥50% on successive biopsies |
| **SD** When all criteria are met. | Change from -49% to +49% | Change from -49% to +49% | Any | Change from -49% to +49% | Change from -49% to +49% | Increase <11.0 g/dL or <50% over baseline, or decrease <2 g/dL | No change in marrow infiltrate |

Abbreviations: CR = complete remission; CLL = chronic lymphocytic leukemia; PD = progressive disease; PR = partial remission; SD = stable disease.

a Spleen size is considered normal if <13 cm. There is no established international consensus of the size of a normal liver. Evaluate the liver size by imaging and manual palpation.

b Normal lymphocyte count should be $<4 \times 10^9$/L. CR also requires absolute neutrophil count to be $\geq 1.5 \times 10^9$/L.

c At least 2 of the parameters of Group A and 1 parameter of group B need to improve if previously abnormal. If only 1 criterion from both Groups A and B is abnormal before receiving study intervention, then at least 1 of those criteria improves after receiving study intervention.

d Sum of the products of 6 or fewer lymph nodes, as evaluated by imaging and physical examination in clinical studies or by physical examination in general practice.

e Appearance of any new lesion, such as enlarged lymph nodes (≥1.5 cm), splenomegaly, hepatomegaly, or other organ infiltrates. Transient increases of lymph node size during treatment with novel inhibitors may occur and should not be counted as PD. Isolated new lymphocytosis occurring early in the treatment course will not be used as criteria for determining PD. Constitutional symptoms alone do not define PD.

f Any lymph node greater than 1.5 cm of any previous site that increases by ≥50% from nadir in greatest determined diameter.

Source: Hallek et al. 2018.

### Additional response criteria

#### *CRi*

CRi is when a participant fulfills all criteria for a CR, with persistent anemia, neutropenia, or thrombocytopenia, and the investigator relates the cytopenia to study intervention and not due to the underlying disease.

#### *nPR*

nPR is when a participant fulfills all criteria for a CR, but the bone marrow biopsy or aspirate shows B-lymphoid nodules with residual disease.

***PR-L***

BTK inhibitors are known to cause lymphocytosis, defined as an increase in the number of blood lymphocytes by 50% or more with at least 5× $10^9$/L B lymphocytes, due to redistribution of lymphocytes.

In BTK inhibitors or compounds with similar mechanism of action, initial absolute lymphocyte count progression with associated PR in other categories during therapy is usually indicative of PR-L (Cheson et al. 2012).

## 8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA.

### 8.2.1. Physical Examinations

A complete physical examination will include, at a minimum, assessments of these systems:

- cardiovascular
- respiratory
- musculoskeletal
- lymphatic, and
- neurological.

The physical examination will include measurement of body temperature and assessment of peripheral lymph nodes.

A complete physical examination may be repeated at the investigator's discretion at any time a participant presents with physical complaints.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

### 8.2.2. Vital Signs

Measure vital signs after the participant has been sitting at least 5 minutes, and before obtaining an ECG tracing, or collection of blood samples for laboratory testing.

### 8.2.3. Electrocardiograms

For each participant, a single 12-lead digital ECG will be collected according to the SoA. The ECG should be recorded before collecting any blood. Participants must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.

ECGs will be interpreted by a qualified physician (the investigator or qualified designee) at the study site as soon after the time of ECG collection as possible, and ideally while the participant is still present, to determine whether the participant meets the study entry criteria and for immediate participant management, should any clinically relevant findings be identified.

If the investigator suspects drug-induced QTcF prolongation or prolongation due to electrolyte abnormalities, the investigator may either discontinue the suspecting drug, switch to another drug that is not associated with QTcF prolongation, or provide electrolyte supplementation, only if it is clinically safe to do so.

Correction of QTc for widened QRS from underlying bundle branch block or other intraventricular conduction delays is allowed. If an individual has a widened QRS, follow these steps

1. calculate the QTc value using locally approved correction factors.
   This calculation may be used if a participant has a QRS duration >110 ms
   *Adjusted QTcF = measured QTcF- [measured QRS-90 ms]*
2. enter the adjusted QTcF into the eCRF.

If a clinically significant finding is identified after enrollment, the investigator in conjunction with the sponsor will determine if the participant can continue in the study and if any change in participant management is needed.

### 8.2.4. Clinical Safety Laboratory Tests

See Section 10.2 for the list of clinical laboratory tests to be performed and the SoA for the timing and frequency.

The investigator must review the laboratory results, document this review, and report any clinically relevant changes occurring during the study as an AE. The laboratory results must be retained with source documents unless a Source Document Agreement or comparable document cites an electronic location that accommodates the expected retention duration.

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 participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 7 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

All protocol-required laboratory assessments, as defined in Section 10.2, must be conducted in accordance with the SoA, standard collection requirements, and laboratory manual.

If laboratory values from non-protocol-specified laboratory assessments performed at an investigator-designated local laboratory require a change in participant management or are considered clinically significant by the investigator, for example, SAE or AE or dose modification, then report the information as an AE.

### 8.2.5. Pregnancy Testing

For individuals of childbearing potential, pregnancy testing must be conducted in accordance with the SoA (Section 1.3.1).

Pregnancy tests may be performed locally.

If a serum pregnancy test is positive, the participant will be permanently discontinued from study intervention (Section 7.1).

Details of all pregnancies in individuals of childbearing potential or partners of childbearing potential will be collected as outlined in Sections 8.3.1 and 8.3.2.

### 8.2.6. Hepatic Safety Monitoring

**Close hepatic monitoring and evaluation**

Liver testing (Section 10.5), including ALT, AST, ALP, TBL, D. Bil, GGT, and CK, should be repeated within 2 to 4 days to confirm the abnormality and to determine if it is increasing or decreasing, if 1 or more of the conditions in this table occur.

| If a participant with baseline results of... | develops the following elevations… |
|---|---|
| ALT or AST <1.5x ULN | ALT or AST ≥5x ULN or<br>ALT or AST ≥3x ULN concurrent with TBL ≥2x ULN |
| ALT or AST ≥1.5x ULN | ALT or AST ≥3x baseline or<br>ALT or AST ≥2x baseline concurrent with TBL ≥2x ULN |

If the abnormality persists or worsens, clinical and laboratory monitoring and evaluation for possible causes of abnormal liver tests should be initiated by the investigator in consultation with the Lilly-designated medical monitor.

At a minimum, this evaluation should include physical examination and a thorough medical history, including symptoms, recent illnesses (for example, heart failure, systemic infection, hypotension, or seizures), history of concomitant medications, including over-the-counter, herbal and dietary supplements, history of alcohol drinking and other substance abuse. In addition, the evaluation should include a blood test for PT-INR; serological tests for viral hepatitis A, B, C, E, autoimmune hepatitis; and an abdominal imaging study, for example, ultrasound or CT scan.

Based on the participant'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
- cytomegalovirus
- Epstein-Barr virus
- acetaminophen levels
- acetaminophen protein adducts
- urine toxicology screen
- Wilson's disease
- blood alcohol levels
- urinary ethyl glucuronide, and
- blood phosphatidyl ethanol.

Based on the circumstances and the investigator's assessment of the participant's clinical condition, the investigator should consider referring the participant for a hepatologist or gastroenterologist consultation, magnetic resonance cholangiopancreatography, endoscopic retrograde cholangiopancreatography, cardiac echocardiogram, or a liver biopsy.

**Additional hepatic safety data collection**

Additional safety data should be collected via the CRF if 1 or more of the following conditions occur:

- discontinuation from study treatment due to a hepatic event or abnormality of liver tests, or
- occurrence of a hepatic event considered to be an SAE.

### 8.2.7. Hepatitis B Virus Monitoring for Reactivation in High-Risk Patients

See Section 5.2 for enrollment criteria.

Individuals enrolled with positive anti-HBc and negative HBsAg and HBV DNA should undergo regular monitoring for viral reactivation by performing testing for HBV DNA by PCR approximately every 2-4 months throughout the study and at 6 months after short-term follow-up.

If HBV DNA becomes positive, consider withholding pirtobrutinib and consulting with a hepatologist or gastroenterologist for further assessment.

### 8.2.8. Monitoring for Infections or Bleeding

**Infections**

Infections, which can be serious, life-threatening, and possibly fatal, are a known risk of BTK inhibitor therapy in this population.

Monitor participants throughout the study for signs of infection, particularly in participants with additional concurrent risk factors, such as heavily pretreated, poor bone marrow function, ongoing neutropenia, or diabetes, who may be at increased risk for serious complications.

The use of prophylactic antimicrobial therapy should be considered in all study participants when clinically appropriate and as allowable by protocol and local label guidance.

**Bleeding**

Bleeding, which can be serious, life-threatening, and possibly fatal, is also a known risk of BTK inhibitor therapy.

For all study participants who require anticoagulation or antiplatelet therapy, as allowed by the protocol and local label guidance, the benefit versus risk of concurrent treatment should be carefully considered.

Participants receiving anticoagulation or antiplatelet therapy should be monitored for signs and symptoms of bleeding throughout the course of the study.

If a participant requires surgery, consider the benefit versus risk of withholding therapy for at least 3 days before and after surgery, depending upon the type of surgery and the risk of bleeding.

## 8.3. Adverse Events, Serious Adverse Events, and Product Complaints

The definitions of the following events can be found in Appendix 3:

- AEs
- SAEs, and
- PCs.

These events will be reported by the participant or, when appropriate, by the participant's legally authorized representative.

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet these definitions and remain responsible for following up events that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention (see Section 7).

Care will be taken not to introduce bias when detecting events. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about event occurrences.

After the initial report, the investigator is required to proactively follow each participant at subsequent visits or contacts. All SAEs and AEs of special interest as defined in Section 8.3.3 will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

For product complaints, the investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature or causality. Further information on follow-up procedures is provided in Appendix 3, Section 10.3.

### 8.3.1. Timing and Mechanism for Collecting Events

This table describes the timing, deadlines, and mechanism for collecting events.

| Event | Collection Start | Collection Stop | Timing for Reporting to Sponsor or Designee | Mechanism for Reporting | Back-Up Method of Reporting |
|---|---|---|---|---|---|
| **Adverse Event** | | | | | |
| AE | Signing of the ICF | Completion of the short-term follow-up visit.<br>Long-term follow-up: only collect AEs related to study treatment or any AEs leading to death | As soon as possible upon site awareness | AE CRF | N/A |
| **Serious Adverse Event** | | | | | |
| SAE and SAE updates – prior to start of study intervention **and** deemed reasonably possibly related to study procedures | Signing of the ICF | Start of intervention | Within 24 hr of awareness | SAE CRF | SAE paper form |
| SAE and SAE updates – after start of study intervention | Start of intervention | Completion of the short-term follow-up visit.<br>Long-term follow-up: only collect SAEs related to study treatment | Within 24 hr of awareness | SAE CRF or SAE paper form | SAE paper form |

| Event | Collection Start | Collection Stop | Timing for Reporting to Sponsor or Designee | Mechanism for Reporting | Back-Up Method of Reporting |
|---|---|---|---|---|---|
| SAE[a] – after participant's study participation has ended **and** the investigator becomes aware | After participant's study participation has ended | N/A | Promptly | SAE paper form | N/A |
| **Pregnancy** | | | | | |
| Pregnancy in participants and partners of participants | After the start of study intervention | Completion of the short-term follow-up visit. | Within 24 hr (see Section 8.3.2) | Pregnancy CRF | Pregnancy paper form |
| **Product Complaints** | | | | | |
| PC associated with an SAE or might have led to an SAE | Start of study intervention | End of study intervention | Within 24 hr of awareness | Product Complaint form | N/A |
| PC not associated with an SAE | Start of study intervention | End of study intervention | Within 1 business day of awareness | Product Complaint form | N/A |
| Updated PC information | — | — | As soon as possible upon site awareness | Originally completed Product Complaint form with all changes signed and dated by the investigator | N/A |
| PC (if investigator becomes aware) | Participation in study has ended | N/A | Promptly | Product Complaint form | |

Abbreviations: AE = adverse event; CRF = case report for; ICF = Informed Consent Form; N/A = not applicable; PC = product complaint; SAE = serious adverse event.

[a] Serious adverse events, including death caused by disease progression, should not be reported unless the investigator deems them to be possibly related to study treatment or study participation.

### 8.3.2. Collection of Pregnancy Information

#### 8.3.2.1. Participants Who Become Pregnant

The investigator will collect pregnancy information on any participant who becomes pregnant while participating in this study. The initial information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a participant's pregnancy.

The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate, and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of gestational age, fetal status (presence or absence of anomalies), or indication for the procedure.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.

A spontaneous abortion (occurring at <20 weeks gestational age) or still birth (occurring at ≥20 weeks gestational age) is always considered to be an SAE and will be reported as such.

Any poststudy pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.3.1. While the investigator is not obligated to actively seek this information in former study participants, the investigator may learn of an SAE through spontaneous reporting.

Any participant who becomes pregnant while participating in the study will discontinue study intervention. If the participant is discontinued from the study, follow the standard discontinuation process and continue directly to the follow-up phase. The follow-up on the pregnancy outcome should continue independent of intervention or study discontinuation.

#### 8.3.2.2. Participants With Partners Who Become Pregnant

**When to collect pregnancy information**

In most circumstances, the investigator will attempt to collect pregnancy information from a participant's partner who becomes pregnant while the participant is in this study.

After learning about a pregnancy in the partner of a study participant, the investigator

- will obtain a consent to release information from the pregnant partner directly, and
- within 24 hours after obtaining this consent, will record pregnancy information on the appropriate form and submit it to the sponsor.

The partner will be followed to determine the outcome of the pregnancy. Information on the status of the mother and neonate will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks after the estimated delivery date. Any termination of the pregnancy will be reported regardless of gestational age, fetal status (presence or absence of anomalies), or indication for the procedure.

**When not to collect pregnancy information**

It is not necessary to collect information about a pregnancy in the partner of a study participant in these circumstances:

- the partner of the study participant was not exposed to the study intervention, or
- the participant did not contribute the sperm or ova that resulted in the pregnancy.

### 8.3.3. Adverse Events of Special Interest

Adverse events of special interest for this study include

- hemorrhage
- cytopenia
- infections, and
- atrial fibrillation/atrial flutter.

More detailed information on these AEs may be found in the IB and prescribing information.

The investigator may consider modifying the dose of pirtobrutinib, for participants experiencing AESI events described in Section 6.6.

**Hemorrhage**

***Causes of hemorrhage in this study population***

Bleeding, mainly low-grade, nonserious events of bruising and bleeding, is a recognized drug class effect of BTK inhibitor therapy.

***Participant monitoring for bleeding***

This study includes routine monitoring of blood count, for cases of bleeding for all participants (Section 1.3).

If a participant shows signs of bruising or bleeding, the investigator should consider checking a coagulation laboratory panel.

**Cytopenia**

Cytopenia is a low level of certain blood cells, such as neutropenia, anemia, or thrombocytopenia.

***Causes of cytopenia in this study population***

Causes of cytopenia include complications from the disease or complications from a participant's therapy. Cytopenia is a recognized drug class effect of BTK inhibitor therapy.

Individuals receiving pirtobrutinib mainly experienced neutropenia followed by anemia and thrombocytopenia.

***Participant monitoring for cytopenia***

This study includes routine hematologic monitoring throughout the study for all participants (Section 1.3).

If a participant develops neutropenia, the investigator should monitor the participant for increased risk of infection, as clinically appropriate.

If a participant develops thrombocytopenia, the investigator should monitor the participant for increased risk of bleeding, as clinically appropriate.

**Infections**

***Causes of infection in this study population***

Increased occurrence or severity of infections risk is a recognized risk of BTK inhibitor therapy. The risks include life-threatening, opportunistic, and fatal infections, including sepsis, and sepsis shock. These risks may increase due to a participant's underlying disease, age, prior treatment history, or comorbidities.

***Participant monitoring for infections***

The investigator will monitor participants throughout the study for signs of infection, particularly those with additional risk factors, such as participants that have poor bone marrow function, ongoing neutropenia, or diabetes.

**Atrial fibrillation/flutter**

***Causes of atrial fibrillation/atrial flutter in this study population***

Atrial fibrillation is a class label risk with BTK inhibitors and is known to occur due to the off-target effect of inhibition of non-BTK kinases.

Cardiovascular comorbidities in older patients and prior chemoimmunotherapy or therapy with BTK inhibitors may increase the risk of arrhythmia.

Patients with significant cardiovascular disease are excluded from participation in this study because they are at higher risk for development of atrial fibrillation or atrial flutter.

***Participant monitoring for atrial fibrillation/atrial flutter***

Participants will undergo regular monitoring through ECGs and physical examination, including vital signs, to detect arrythmia.

## 8.4. Pharmacokinetics

Collect blood samples from all participants at the visits and times specified in the SoA (Section 1.3.2). Additional PK samples may also be collected when considered necessary by the investigator to understand exposure in relationship to possible safety.

Blood for PK assessment should be collected even if study intervention is held for the next cycle.

Samples will be analyzed at a laboratory approved by the sponsor. Concentrations of pirtobrutinib will be assayed using a validated bioanalytical assay.

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 the date and time of the most recent dose before the PK blood draw must be recorded. In addition, after C1D1, record the time and date of the 2 doses that occur before the PK blood draw.

Sample retention is described in Section 10.1.12.

## 8.5. Pharmacodynamics

Refer to Section 8.7.

## 8.6. Genetics

Refer to Section 8.7.

## 8.7. Biomarkers

Biomarker research is performed to address questions of relevance to drug disposition, target engagement, pharmacodynamics, mechanism of action, early markers of drug efficacy, 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, nucleic acids like DNA and RNA, cell free DNA, proteins, lipids, and other cellular elements. Samples may also be used to support the development of new diagnostic tools or assays.

Results of CCI will not be provided to the investigative sites.

Sample retention is described in Section 10.1.12.


## 8.8. Immunogenicity Assessments

This section is not applicable for this study.

## 8.9. Medical Resource Utilization and Health Economics

Medical resource utilization and health economics parameters are not evaluated in this study.

# 9. Statistical Considerations

The statistical analysis plan will be finalized prior to first participant first visit, and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints, including primary and secondary endpoints.

## 9.1. Statistical Hypothesis

Pirtobrutinib 200 mg will provide a clinically meaningful increase in ORR over pirtobrutininb CCI in participants with relapsed or refractory CLL/SLL. The statistical hypothesis will be evaluated based on the ORR difference comparing 200 mg versus CCI and 200 mg versus CCI and will be further detailed in the SAP.

## 9.2. Analyses Sets

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

| Population | Description |
|---|---|
| ITT | All randomized participants, even if they do not take the assigned treatment, do not receive the correct treatment, or otherwise do not follow the protocol. Participants will be analyzed according to the treatment group they were assigned to regardless of what actual treatment they receive |
| Safety | All randomized participants who take at least 1 dose (including a partial dose) of study intervention. Analysis of safety data will be based on the actual intervention a participant received on the first study drug administration, regardless of which intervention they were randomized to receive ("as treated") |

## 9.3. Statistical Analyses

### 9.3.1. General Considerations

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

All CI on point estimates will be given at a CCI confidence level unless otherwise stated.

Continuous variables, such as number of participants, mean, median, standard deviation, minimum, and maximum, will be summarized using descriptive statistics.

Categorical variables will be summarized by frequency and its corresponding percentage.

Any change to the data analysis and methods described in the protocol will require an amendment only if it changes a principal feature of the protocol.

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.

More details for the analyses will be provided in the SAP. Any other changes to the data analysis methods described in the protocol or SAP will be described and justified in the clinical study report.

### 9.3.2. Treatment Group Comparability

#### 9.3.2.1. Participant Disposition

A detailed description of participant disposition by treatment group will be provided, including the number of participants randomized to the study, treated in the study, discontinued from treatment with reason for discontinuation, and discontinued from the study with reason for discontinuation.

#### 9.3.2.2. Participant Characteristics

A summary of baseline demographics and disease characteristics, historical diagnoses, preexisting conditions, and prior therapies will be reported by treatment group using descriptive statistics.

#### 9.3.2.3. Concomitant Therapy

A summary of concomitant medications by treatment group will be provided.

#### 9.3.2.4. Prior and Subsequent Anticancer Therapy

Prior and subsequent anticancer therapy used to treat CLL/SLL will be summarized by treatment group for applicable participants.

#### 9.3.2.5. Extent of Exposure

The duration of therapy, dose modifications, and dose intensity for each treatment group will be summarized.

### 9.3.3. Primary Endpoints Analysis

The primary endpoint is ORR as assessed by investigator per iwCLL 2018 criteria (Section 8.1.4). ORR is defined as the proportion of participants who achieve the BOR of CR, CRi, nPR, or PR at or before the initiation of subsequent anticancer therapy.

The primary analysis will be conducted in the ITT population.

The ORR and the corresponding CCI [redacted] will be summarized for each treatment group. CCI [redacted] will be used to test for differences in ORR. CCI [redacted] on the point estimates of the differences in ORR will be summarized.

Further details will be provided in the SAP.

### 9.3.4. Secondary Endpoints Analysis

**Duration of response**

Investigator-assessed DOR is defined as the time from first documented response of CR, CRi, nPR, or PR to the first documentation of disease progression (per iwCLL 2018 criteria, Section 8.1.3) or death from any cause. Following first documentation of CR, CRi, nPR, or PR, participants who are alive and without documented disease progression at the time of the data analysis cutoff date will be censored. A detailed DOR event/censoring scheme will be provided in the SAP.

Median DOR and its CCI , and DOR rates and associated CCI at selected timepoints, for each treatment group will be estimated CCI CCI

**Safety analysis**

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 intervention administration.

AEs will be graded by the investigator according to the NCI CTCAE v5.0 for nonhematologic and hematologic AEs. Each AE verbatim term will be coded to a System Organ Class and a Preferred Term using the MedDRA.

All TEAEs will be summarized by treatment group, including severity and relationship to study intervention.

Summaries by treatment group will be provided for the following, but not limited to

- ≥Grade 3 AESIs
- ≥Grade 3 TEAEs
- SAEs
- discontinuations due to an AE
- dose interruptions due to an AE, and
- dose reductions due to an AE.

Estimates of key safety measures will be summarized with CCI for each treatment group.

Clinical laboratory parameters will be summarized by treatment and the worst postbaseline toxicity grade that occurs during the treatment period.

Serum immunoglobulins (IgA, IgG, and IgM) will be summarized with descriptive statistics. Participants who receive IV immunoglobulin during the study will be excluded from the summary for IgG.

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

### 9.3.5. Pharmacokinetic and 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.

### 9.3.6. Other Analyses

#### 9.3.6.1. Other Efficacy Analysis

**Progression-free survival**

Investigator-assessed PFS is defined as the time from randomization until documented disease progression (per iwCLL 2018 criteria) or death from any cause, whichever occurs first. Participants known to be alive and without documented disease progression at the time of the data analysis cutoff date will be censored at the date of the last adequate disease assessment. A detailed PFS event or censoring scheme will be provided in the SAP.

Median PFS and its CCI and PFS rates and associated CCI at selected timepoints, for each treatment group will be estimated using the CCI

**Overall survival**

OS is defined as the time from randomization until death from any cause. If the participant is alive or lost to follow-up at the time of the data analysis cutoff date, OS data will be censored on the last date the participant is known to be alive. A detailed OS event or censoring scheme will be provided in the SAP. Median OS and its CCI and OS rates and associated CCI at selected timepoints, for each treatment group will be estimated using CCI

#### 9.3.6.2. Biomarker Analysis

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

#### 9.3.6.3. Subgroup Analyses

Subgroup analyses will be performed if deemed necessary. The details will be in the SAP.

## 9.4. Interim Analysis

No interim analyses are planned for this study. If an unplanned interim analysis is deemed necessary for reasons other than a safety concern, the protocol must be amended.

An AC internal to Lilly will conduct a periodic safety and efficacy data review during the study (Section 10.1.5).

## 9.5. Sample Size Determination

Approximately 249 participants will be randomly assigned in a CCI ratio to receive either pirtobrutinib 200 mg, CCI approximately CCI participants per dose level.

The superiority of pirtobrutinib 200 mg versus CCI as measured by investigator-assessed ORR will be tested using a CCI With CCI participants per dose level, there is CCI power to detect a difference in ORR, assuming a CCI ORR with pirtobrutinib 200 mg and CCI ORR CCI Efficacy boundary on the difference in ORR is approximately CCI.

CCI

The CCI ORR assumed for pirtobrutinib 200 mg is based on the results from Study 18001 for participants with CLL/SLL who were previously treated with BTK inhibitors and received pirtobrutinib at a starting dose of 200 mg. Given limited efficacy data from Study 18001 at lower dose levels, a CCI ORR was assumed for CCI , since a CCI shift in true ORR (efficacy boundary of CCI is the minimal clinically meaningful difference in which the efficacy at lower doses is clearly worse than the efficacy of pirtobrutinib 200 mg.

Additionally, a sample size of CCI participants per dose level will provide approximately CCI power to detect a difference in the occurrence of Grade 3 or higher treatment-emergent AESIs between any two dose levels, when the assumed incidence rates are CCI CCI These comparisons on treatment-emergent AESIs will not be CCI

# 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 (CIOMS) International Ethical Guidelines
- applicable ICH GCP Guidelines, and
- applicable laws and regulations.

The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents, for example, 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 amendments 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 participants.

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for

- 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 study conduct for participants under their responsibility and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European Regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations, and
- reporting to the sponsor or designee significant issues related to participant safety, participant rights, or data integrity.

Investigator sites are compensated for participation in the study as detailed in the Clinical Trial Agreement.

### 10.1.2. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are

responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

### 10.1.3. Informed Consent Process

The investigator or the investigator's representative will explain the nature of the study, including the risks and benefits, to the potential participant and, if applicable, the potential participant's legally authorized representative and answer all questions regarding the study.

Potential participants must be informed that their participation is voluntary. Participants and, if applicable, 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, privacy and data protection 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 participant was entered in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Revised consents must be appropriately obtained using the correct approved ICFs for applicable study participants in accordance with sponsor and ERB consenting guidance.

A copy of the ICF(s) must be provided to the participant and, if applicable, the participant's legally authorized representative, and is kept on file.

Participants who are rescreened are required to sign a new ICF.

### 10.1.4. 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).

### 10.1.5. Committees Structure

An AC internal to Lilly will review safety and efficacy data during the study.

The AC will be fully independent from the study team and will include, at a minimum, a Lilly medical physician and a statistician.

Details about the AC membership, purpose, responsibilities, and operation will be described in an AC charter, which will be approved before first participant visit.

Study sites will receive information about interim results ONLY if they need to know for the safety of their participants. The AC will determine whether there are sufficient safety concerns to justify a change in the conduct of the study or the termination of study treatment or enrollment.

### 10.1.6. 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 CCI [redacted].

### 10.1.7. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRFs unless transmitted to the sponsor or designee electronically, for example, laboratory data. The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF. This includes laboratory tests, medical records, and clinical notes.

The investigator must review and confirm that data entries are accurate and complete throughout the duration of the study, by physically or electronically signing the CRF, as instructed by the sponsor. All completed CRFs must be signed prior to archival.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct or remote access to source documents.

Quality tolerance limits will be predefined to identify systematic issues that can impact participant safety and/or reliability of study results. These predefined parameters will be monitored during the study and important excursions from the quality tolerance limits and remedial actions taken will be summarized in the clinical study report.

Monitoring details describing strategy, for example, risk-based initiatives in operations and quality, such as risk management and mitigation strategies and analytical risk-based monitoring, methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques are provided in the Monitoring Plan.

The sponsor or designee is responsible for the data management of this study, including quality checking of the data.

The sponsor assumes accountability for actions delegated to other individuals, for example, contract research organizations.

The sponsor or designee will perform monitoring to confirm that data transcribed into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants 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 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.

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

**Data capture system**

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

An EDC will be used in this study for the collection of CRF 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 CRF.

Data collected via the sponsor-provided data capture system(s) will be stored at third party. The investigator will have continuous access to the data during the study and until decommissioning of the data capture system. Prior to decommissioning, the investigator will receive or access an archival copy of pertinent data for retention.

Data managed by a central vendor, such as laboratory test data, will be stored electronically in the central vendor's database system and reports will be provided to the investigator for review and retention. Data will subsequently be transferred from the central vendor to the sponsor data warehouse.

Data from complaint forms submitted to the sponsor will be encoded and stored in the global product complaint management system.

### 10.1.8. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on or entered in the CRF and 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.

Definition of what constitutes source data can be found in the site confirmation of source data.

### 10.1.9. Study and Site Start and Closure

**Study start**

The study start date is the date on which the clinical study will be open for recruitment of participants.

**First act of recruitment**

The first act of recruitment is the opening of the first site.

**Study or site termination**

The sponsor or sponsor's designee 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

- for study termination due to discontinuation of further study intervention development
- for site termination due 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, evaluated after a reasonable amount of time of participants by the investigator, or
    - total number of participants included earlier than expected.

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 participant and should assure appropriate participant therapy and/or follow-up.

### 10.1.10. Publication Policy

In accordance with the sponsor’s publication policy, the results of this study will be submitted for publication by a peer-reviewed journal.

### 10.1.11. Investigator Information

Researchers with appropriate education, training, and experience, as determined by the sponsor, will participate as investigators in this clinical trial.

### 10.1.12. Sample Retention

Sample retention 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.

| Sample Type | Custodian | Maximum Retention Period after Last Participant Visit[a] |
|---|---|---|
| Pharmacokinetics | Sponsor or designee | 1 year |
| Biomarkers | Sponsor or designee | 15 years |

[a] Sample retention periods may differ dependent upon local regulations.

## 10.2. Appendix 2: Clinical Laboratory Tests

The tests detailed in the table below will be performed by the local laboratory or a Lilly-designated laboratory.

In circumstances where the sponsor approves local laboratory testing in lieu of central laboratory testing, the local laboratory must be qualified in accordance with applicable local regulations.

Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Investigators must document their review of the laboratory safety results.

| Clinical Laboratory Tests | Comments |
|---|---|
| **Hematology** | Locally performed |
| **Hemoglobin** | |
| Hematocrit | |
| Erythrocyte count (RBCs - red blood cells) | |
| Leukocytes (WBCs - white blood cells) | |
| Differential | |
| Percent and/or absolute count of: | |
| Neutrophils | Neutrophils reported by automated differential hematology instruments may 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 recorded on the CRF |
| Lymphocytes | |
| Monocytes | |
| Eosinophils | |
| Basophils | |
| Platelets | |
| Coagulation | Locally performed |
| International normalized ratio (INR) or prothrombin time (PT) | |
| Activated partial thromboplastin time (aPTT) or PTT | |
| **Clinical chemistry** | Locally performed |
| Sodium | |
| Potassium | |
| Chloride | |
| Blood urea nitrogen (BUN) or blood urea | |
| Creatinine | |
| Creatine kinase (CK) | |
| Alkaline phosphatase (ALP) | |
| Alanine aminotransferase (ALT) | |
| Aspartate aminotransferase (AST) | |
| Total bilirubin | |

| Clinical Laboratory Tests | Comments |
|---|---|
| Direct bilirubin | |
| Total protein | |
| Albumin | |
| Calcium (serum) | |
| Magnesium | |
| Phosphorus | |
| Uric acid | |
| Lactate dehydrogenase (LDH) | |
| Glucose (random) | |
| **Urinalysis** | Locally performed |
| Specific gravity | |
| pH | |
| Protein | |
| Glucose | |
| Ketones | |
| Bilirubin | |
| Urobilinogen | |
| Blood | |
| Nitrite | |
| Urine leukocyte esterase | Urine microscopy may be used in the place of the urine leukocyte esterase assessment to test for the presence of WBCs |
| Microscopic examination of sediment | If clinically indicated |
| **Pregnancy test** | Locally performed |
| Serum pregnancy | For participants of childbearing potential |
| Urine pregnancy | For participants of childbearing potential |
| **Hepatitis serology and CMV** | Locally performed |
| Hepatitis B Virus (HBV) testing | All participants should have serology, including hepatitis B surface antigen and hepatitis B core total antibody **or** an HBV DNA |
| HBV DNA | Collect only if necessary to determine eligibility as per Section 5.2 |
| Hepatitis C Virus (HCV) testing | |
| CMV PCR | |
| **Pharmacokinetic samples**<br>pirtobrutinib concentration | Assayed by Lilly-designated laboratory.<br>Results will not be provided to the investigative sites |
| **Immunoglobulin panel** | Locally performed |
| IgA | |
| IgE | |
| IgG | |
| IgM | |

CCI

## 10.3. Appendix 3: Adverse Events and Serious Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting

### 10.3.1. Definition of AE

- An AE is any untoward medical occurrence in a participant administered a pharmaceutical product and which does not necessarily have a causal relationship with the study intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal (investigational) product, or investigational combination product, whether or not related to the medicinal (investigational) product or investigational combination 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 signs 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.
- Lack of efficacy or failure of expected pharmacological action per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

**Events NOT meeting the AE definition**

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- The disease or disorder being studied or expected progression, signs, or symptoms of the disease or disorder being studied, unless more severe than expected for the participant's condition.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

### 10.3.2. Definition of SAE

**An SAE is defined as any untoward medical occurrence that, at any dose, meets 1 or more of the criteria listed:**

- Results in death
- Is life-threatening
    - The term *life-threatening* in the definition of *serious* refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization
    - In general, hospitalization signifies that the participant has been admitted to hospital or emergency ward (usually involving at least an overnight stay) for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.
    - Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.
- Results in persistent disability/incapacity
    - The term disability means a substantial disruption of a person's ability to conduct normal life functions.
    - This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma, for example, sprained ankle, which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- Is a congenital anomaly/birth defect
    - Abnormal pregnancy outcomes, for example, spontaneous abortion, fetal death, stillbirth, congenital anomalies, and ectopic pregnancy, are considered SAEs.
- Other situations
    - Medical or scientific judgment should be exercised by the investigator in deciding whether SAE 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 participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
    - Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood

dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

### 10.3.3. Definition of Product Complaints

**Product complaint**

A product complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a study intervention. When the ability to use the study intervention safely is impacted, the following are also product complaints:

- deficiencies in labeling information, and
- use errors for device or drug-device combination products due to ergonomic design elements of the product.

Product complaints related to study interventions used in clinical trials are collected to ensure the safety of participants, monitor quality, and to facilitate process and product improvements.

If the participant identifies a product complaint or a problem with the study intervention, investigators will instruct participants to contact the site as soon as possible so that the situation can be assessed.

An event may meet the definition of both a product complaint and an AE/SAE. In such cases, it should be reported as both a product complaint and as an AE/SAE.

Device deficiencies are product complaints.

### 10.3.4. Recording and Follow-Up of AE and/or SAE and Product Complaints

**AE, SAE, and product complaint recording**

When an AE/SAE/product complaint occurs, it is the responsibility of the investigator to review all documentation, for example, hospital progress notes, laboratory reports, and diagnostics reports, related to the event.

The investigator will then record all relevant AE/SAE/product complaint information in the participant's medical records, in accordance with the investigator's normal clinical practice. AE/SAE information is reported on the appropriate CRF page, and product complaint information is reported on the Product Complaint form.

Note: An event may meet the definition of both a product complaint and an AE/SAE. In such cases, it should be reported as both a product complaint and as an AE/SAE.

It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the sponsor or designee in lieu of completion of the CRF page for AE/SAE and the Product Complaint form for product complaints.

There may be instances when copies of medical records for certain cases are requested by the sponsor or designee. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the sponsor or designee.

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

**Assessment of intensity**

The investigator will use CTCAE version 5.0 (NCI 2018) to assign AE severity grades.

**Assessment of causality**

The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship.

A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.

The investigator will also consult the IB and Product Information in their assessment.

The investigator **must** review and provide an assessment of causality for each AE/SAE and document this in the medical notes.

There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor or designee. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor or designee.

The investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

**Follow-up of AEs and SAEs**

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor or designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

### 10.3.5. Reporting of SAEs

**SAE reporting via an electronic data collection tool**

The primary mechanism for reporting an SAE will be the electronic data collection tool.

If the electronic system is unavailable, then the site will use the SAE paper form (see next section) in order to report the event within 24 hours.

The site will enter the SAE data into the electronic system as soon as it becomes available.

After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.

If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on an SAE paper form (see next section) or to the medical monitor by telephone.

Contacts for SAE reporting can be found in the SAE form.

**SAE reporting via paper form**

Facsimile transmission of the SAE paper form is the preferred method to transmit this information to the medical monitor.

Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.

Contacts for SAE reporting can be found in SAE form.

### 10.3.6. Regulatory Reporting Requirements

**SAE regulatory reporting**

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study intervention under clinical investigation are met.

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 will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (for example, summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

# 10.4. Appendix 4: Contraceptive and Barrier Guidance

## 10.4.1. Definitions

| Word/Phrase | Definition |
|---|---|
| Individuals assigned female at birth (AFAB) | Individuals assigned the female sex based on external genitalia and/or genetic or medical information. In addition, if these individuals are of reproductive potential, they are potentially capable of gestating a fetus and thus are capable of exposing an egg, embryo, or fetus to study drug or drug effects. |
| Individuals assigned male at birth (AMAB) | Individuals assigned the male sex based on external genitalia and/or genetic or medical information. In addition, if these individuals are of reproductive potential, they are not capable of gestating a fetus, but are capable of exposing a fetus to study drug or drug effects via their semen. Individuals AMAB are considered to be not of reproductive potential if they have had orchiectomy (orchidectomy) with or without penectomy, confirmed by operative note. |
| Individuals of childbearing potential (IOCBP)[a] | Adult individuals AFAB are considered IOCBP unless they are INOCBP.<br>Note: Individuals AFAB who are receiving hormone therapy as part of gender transition are considered IOCBP unless they meet the conditions outlined below for INOCBP. |
| Individuals not of childbearing potential (INOCBP)[b] | Individuals AFAB are considered INOCBP if they are not capable of producing ova or embryo and/or are not capable of potentially gestating a fetus. Such individuals include those who<br>• have a congenital anomaly, such as Müllerian agenesis, resulting in confirmed infertility<br>• are infertile due to surgical sterilization, or<br>• are menopausal.<br>Acceptable surgical sterilization methods are hysterectomy, bilateral salpingo-oophorectomy, bilateral salpingectomy, or bilateral oophorectomy. |
| Menopausal state[c] | The menopausal state is defined as an individual<br>• at any age at least 6 weeks post-surgical bilateral oophorectomy with or without hysterectomy, confirmed by operative note; or<br>• aged at least 40 years and up to 55 years with an intact uterus, not on hormone therapy[c], who has had cessation of menses for at least 12 consecutive months without an alternative medical cause, AND with a follicle-stimulating hormone ≥40 mIU/mL; or<br>• 55 years or older not on hormone therapy, who has had at least 12 months of spontaneous amenorrhea, or<br>• aged at least 55 years with a diagnosis of menopause prior to starting hormone replacement therapy. |

[a] IOCBP is inclusive of the concept of women of childbearing potential (WOCBP or WCBP), a term often used in literature and regulatory guidance documents.

[b] INOCBP is inclusive of the concept of women not of childbearing potential (WNOBCP).

[c] The individual should not be taking medications during amenorrhea, such as oral contraceptives, hormone replacement therapy (HRT), gonadotropin-releasing hormone, anti-estrogens, selective estrogen receptor modulators, or chemotherapy that could induce transient amenorrhea. Individuals on HRT and those whose menopausal status cannot be confirmed will be required to comply with the protocol contraception requirements if they wish to continue HRT during the study. Otherwise they must discontinue HRT to allow confirmation of menopausal status before study enrollment.

### 10.4.2. Contraception Guidance

**Guidance for individuals of childbearing potential**

IOCBP who are completely abstinent as their preferred and usual lifestyle, or exclusively engage in sexual relations with other individual(s) who are AFAB as their preferred and usual lifestyle must follow the rules in this table.

| IOCBP must… | IOCBP must not… |
|---|---|
| agree to either remain abstinent or exclusively engage in sexual relations with other individual(s) who are AFAB, and not plan a pregnancy during the study | • use periodic abstinence methods<br>  ○ calendar<br>  ○ ovulation<br>  ○ symptothermal, or<br>  ○ post-ovulation<br>• declare abstinence just for the duration of a trial, or<br>• use the withdrawal method |

IOCBP who are NOT completely abstinent as their preferred and usual lifestyle, or who do NOT exclusively engage in sexual relations with other individual(s) who are AFAB as their preferred and usual lifestyle, must agree to use 2 methods of effective contraception, where at least 1 method must be highly effective. These methods of contraception must be used during the study and for at least 30 days after the last dose of the study intervention.

**Guidance for individuals assigned male at birth**

| Participant Population | Contraception Guidance |
|---|---|
| All individuals AMAB… | should refrain from sperm donation for the duration of the study and for 30 days after the last dose of the study intervention. |
| Individuals AMAB with partner(s) who are IOCBP[a]… | must<br>• remain abstinent (if this is their preferred and usual lifestyle), or<br>• use condoms and at least 1 additional effective method of contraception for the duration of the study and for 1 week after the last dose of the study intervention. |
| Individuals AMAB with partner(s) who are pregnant[a]… | must<br>• remain abstinent (if this is their preferred and usual lifestyle), or<br>• use condoms for the duration of the study and for 1 week after the last dose of the study intervention. |
| Individuals AMAB who exclusively engage in sexual relations with other individual(s) who are AMAB, as their preferred and usual lifestyle… | are not required to use contraception. |

[a] Individuals AMAB who have undergone orchiectomy but not penectomy must use condoms during sex, but the partner who is IOCBP is not required to use an additional form of contraception. Individuals AMAB who have undergone orchiectomy and penectomy are not required to use condoms.

**Examples of different methods of contraception**

| Methods | Examples |
|---|---|

| | |
|---|---|
| Highly effective contraception (less than 1% failure rate) | • fallopian tubal sterilization methods other than bilateral salpingectomy (laparoscopic bipolar electrocoagulation, plastic ring application on the uterine tubes, fallopian tube ligation, hysteroscopic sterilization). Note: Bilateral salpingectomy is indicative of permanent sterilization. Please see the INOCBP definition above<br>• combination oral contraceptive pill<br>• progestin-only contraceptive pill (mini-pill)<br>• implanted contraceptives<br>• injected contraceptives<br>• contraceptive patch (only individuals <198 pounds or 90 kg)<br>• total abstinence<br>• sexual relationships exclusively between individuals who are assigned the same sex at birth<br>• vasectomy – for individuals AMAB in clinical trials and for the partner of an individual AFAB, if only sexual partner<br>• fallopian tube implants, if confirmed by hysterosalpingogram<br>• vaginal ring containing combination hormone medication, or<br>• intrauterine devices |
| Effective contraception | • penile condom with spermicide<br>• vaginal condom with spermicide<br>• diaphragm with spermicide<br>• cervical sponge with spermicide, or<br>• cervical cap with spermicide<br>Note: Penile and vaginal condoms should not be used in combination. |
| Ineffective methods of contraception whether used alone or in any combination | • spermicide alone<br>• periodic abstinence<br>• fertility awareness (calendar method, temperature method, cervical mucus, or symptothermal)<br>• withdrawal<br>• postcoital douche, or<br>• lactational amenorrhea |

## 10.5. Appendix 5: Liver Safety: Suggested Actions and Follow-Up Assessments

See Section 8.2.6 for guidance on appropriate test selection.

Perform these tests at a local laboratory. Based on availability and investigator assessment of these tests, multiple local laboratories may be needed. All local laboratories must be qualified in accordance with applicable local regulations.

| **Hepatic Hematology Panel** | **Hepatic Clinical Chemistry Panel** |
|---|---|
| Hemoglobin | Total bilirubin |
| Hematocrit | Direct bilirubin |
| Erythrocytes (RBCs - red blood cells) | Alkaline phosphatase (ALP) |
| Leukocytes (WBCs - white blood cells) | Alanine aminotransferase (ALT) |
| Differential: | Aspartate aminotransferase (AST) |
| Neutrophils | Gamma-glutamyl transferase (GGT) |
| Lymphocytes | Creatine kinase (CK) |
| Monocytes | **Other Chemistry** |
| Basophils | Acetaminophen |
| Eosinophils | Acetaminophen protein adducts[a] |
| Platelets | Alkaline phosphatase isoenzymes |
| Cell morphology (RBC and WBC) | Ceruloplasmin |
| **Hepatic Coagulation Panel** | Copper |
| Prothrombin time, INR (PT-INR) | Ethyl alcohol (ethanol, EtOH) |
| **Hepatitis A virus (HAV) testing** | Haptoglobin |
| HAV total antibody[b] | Immunoglobulin IgA (quantitative) |
| HAV IgM antibody | Immunoglobulin IgG (quantitative) |
| **Hepatitis B virus (HBV) testing** | Immunoglobulin IgM (quantitative) |
| Hepatitis B surface antigen (HBsAg) | Phosphatidylethanol (PEth) |
| Hepatitis B surface antibody (anti-HBs) | **Urine Chemistry** |
| Hepatitis B core total antibody (anti-HBc) | Drug screen |
| Hepatitis B core IgM antibody | Ethyl glucuronide (EtG) |
| HBV DNA[c] | **Other Serology** |
| **Hepatitis C virus (HCV) testing** | Anti-nuclear antibody (ANA) |
| HCV total antibody[b] | Anti-smooth muscle antibody (ASMA) or anti-actin antibody |
| HCV RNA[c] | **Epstein-Barr virus (EBV) testing** |
| **Hepatitis D virus (HDV) testing**[d] | EBV antibody |
| HDV total antibody[b] | EBV DNA[c] |
| HDV IgM antibody | **Cytomegalovirus (CMV) testing** |
| HDV RNA[c] | CMV antibody |
| **Hepatitis E virus (HEV) testing** | CMV DNA[c] |
| HEV IgG antibody | **Herpes simplex virus (HSV) testing** |
| HEV IgM antibody | HSV (Type 1 and 2) antibody |
| HEV RNA[c] | HSV (Type 1 and 2) DNA[c] |
| **Microbiology Culture** | Liver kidney microsomal type 1 (LKM-1) antibody |
| Blood | |
| Urine | |

[a] Availability of acetaminophen protein adducts testing is limited. Testing may be performed at the central lab, if needed.

[b] If lab does not offer total antibody testing, IgG and IgM are acceptable substitutes.

[c] Reflex/confirmation dependent on regulatory requirements or testing availability, or both.

[d] If HDV testing is not available, HBV testing may be sufficient. If HBV testing is positive, consult with the Lilly-designated medical monitor.

## 10.6. Appendix 6: Region- or Country-Specific Requirements

### 10.6.1. European Union

The study will be conducted in accordance with the Regulation (EU) No 536/2014.

**Regulatory reporting requirements**

The sponsor has processes for safety reports for identification, recording, and expedited reporting of SUSARs according to EU regulatory requirements. The sponsor will comply with applicable regulatory requirements relating to safety reporting to the regulatory authority, per European Union Clinical Trial Regulation 536/2014 submission of SUSARs to the EudraVigilance database.

### 10.6.2. Germany

The revised text in the following sections shows the changes applicable for adult participants at study sites in Germany. This table describes the changes and provides a rationale for the changes.

| Protocol Section Number and Name | Description of the Change | Brief Rationale |
|---|---|---|
| 7.2. Participant Discontinuation/Withdrawal from the Study<br>8.3. Adverse Events, Serious Adverse Events, and Product Complaints<br>10.1.3. Informed Consent Process<br>10.9. Appendix 9. Abbreviations and Definitions | Deleted references to "legally authorized representative," "legal guardian," "parents" | The German Drug Law (Arzneimittelgesetz – AMG) with reference to EU Regulation 536/2014 requires that adult participants act on their own behalf and provide their own written informed consent. If written consent is not possible, verbal consent with a witness is acceptable. No legal representative consent is accepted |

Additions are identified by underscore, and deletions are identified by ~~strikethrough format~~.

### 7.2. Participant Discontinuation from Treatment and Withdrawal from the Study

A participant may withdraw from treatment or the study:

- at any time at the participant's own request for any reason or without providing any reason
- ~~at the request of the participant's designee, for example, participant's legally authorized representative~~

### 8.3. Adverse Events, Serious Adverse Events, and Product Complaints

The definitions of the following events can be found in Appendix 3:

- AEs
- SAEs, and
- PCs.

These events will be reported by the participant~~, or, when appropriate, by the participant's legally authorized representative~~.

### 10.1.3. Informed Consent Process

The investigator or the investigator's representative will explain the nature of the study, including the risks and benefits, to the potential participant ~~and if applicable, the potential participant's legally authorized representative~~, and answer all questions regarding the study.

Potential participants must be informed that their participation is voluntary. Participants~~, and if applicable, 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, privacy and data protection 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 participant was entered in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Revised consents must be appropriately obtained using the correct approved ICFs for applicable study participants in accordance with sponsor and ERB consenting guidance.

A copy of the ICF(s) must be provided to the participant~~, and if applicable, the participant's legally authorized representative,~~ and is kept on file.

Participants who are rescreened are required to sign a new ICF.

## 10.9. Appendix 9: Abbreviations and Definitions

| | |
|---|---|
| **enter** | Participants entered into a study are those who sign the informed consent form directly ~~or through their legally acceptable representatives.~~ |

### 10.6.3. France

The revised text in the following sections show the changes applicable for adult participants at study sites in France. This table describes the changes and provides a rationale for the changes.

| Protocol Section Number and Name | Description of the Change | Brief Rationale |
|---|---|---|
| 7.2. Participant Discontinuation/Withdrawal from the Study<br>8.3. Adverse Events, Serious Adverse Events, and Product Complaints<br>10.1.3. Informed Consent Process<br>10.9. Appendix 9. Abbreviations and Definitions | Deleted references to "legally authorized representative," "legal guardian," "parents" | Article 31 of Regulation (EU) No. 2014/536 of 16 April 2014 and Article L1121-8 of French Public Health Code requires that adult participants act on their own behalf and provide their own written informed consent. If written consent is not possible, verbal consent with a witness is acceptable. No legal representative consent is accepted |

Additions are identified by <u>underscore</u>, and deletions are identified by ~~strikethrough format~~.

### 7.2. Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from treatment or the study:

- at any time at the participant's own request for any reason or without providing any reason
- ~~at the request of the participant's designee, for example, participant's legally authorized representative~~

### 8.3. Adverse Events, Serious Adverse Events, and Product Complaints

The definitions of the following events can be found in Appendix 3:

- AEs
- SAEs, and
- PCs.

These events will be reported by the participant~~, or, when appropriate, by the participant's legally authorized representative~~.

### 10.1.3. Informed Consent Process

The investigator or the investigator's representative will explain the nature of the study, including the risks and benefits, to the potential participant ~~and if applicable, the potential participant's legally authorized representative~~, and answer all questions regarding the study.

Potential participants must be informed that their participation is voluntary. Participants~~, and if applicable, 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, privacy and data protection 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 participant was entered in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Revised consents must be appropriately obtained using the correct approved ICFs for applicable study participants in accordance with sponsor and ERB consenting guidance.

A copy of the ICF(s) must be provided to the participant~~, and if applicable, the participant's legally authorized representative,~~ and is kept on file.

Participants who are rescreened are required to sign a new ICF.

### 10.9. Appendix 9: Abbreviations and Definitions

| | |
|---|---|
| **enter** | Participants entered into a study are those who sign the informed consent form directly ~~or through their legally acceptable representatives.~~ |

## 10.7. Appendix 7: Provisions for Changes in Study Conduct during Exceptional Circumstances

**Implementation of this appendix**

The changes to procedures described in this appendix are temporary measures intended to be used only during specific time periods as directed by the sponsor in partnership with the investigator.

In an exceptional circumstance, the sponsor's procedures ensure that relevant parties are kept informed of changes to the design and conduct of the study.

**Exceptional circumstances**

Exceptional circumstances are rare events that may cause disruptions to the conduct of the study. Examples include pandemics or natural disasters. These disruptions may limit the ability of the investigators or participants, or both, to attend on-site visits or to conduct planned study procedures.

**Implementing changes under exceptional circumstances**

In an exceptional circumstance, after receiving the sponsor's written approval, sites may implement changes if permitted by local regulations.

After approval by local Ethical Review Boards, regulatory bodies, and any other relevant local authorities, implementation of these exceptional circumstance changes will not typically require additional notification to these groups, unless they have specific requirements in which notification is required, for example, upon implementation and suspension of changes. All approvals and notifications must be retained in the study records.

If the sponsor grants written approval for changes in study conduct, the sponsor will also provide additional written guidance, if needed.

**Considerations for making a change**

The prevailing consideration for making a change is ensuring the safety of study participants. Additional important considerations for making a change are compliance with GCP, enabling participants to continue safely in the study and maintaining the integrity of the study.

**Informed consent**

Additional consent from the participant will be obtained, if required, for

- participation in remote visits, as defined in Section "Remote Visits"
- a change in the method of study intervention administration
- dispensation of additional study intervention during an extended treatment period
- alternate delivery of study intervention and ancillary supplies, and
- provision of their personal or medical information required prior to implementation of these activities.

**Changes in study conduct during exceptional circumstances**

Changes in study conduct not described in this appendix, or not consistent with applicable local regulations, are not allowed.

The following changes in study conduct will not be considered protocol deviations.

***Remote visits***

*Types of remote visits*

Telemedicine - Telephone or technology-assisted virtual visits, or both, are acceptable to complete appropriate assessments. Assessments to be completed in this manner include, but are not limited to, concomitant medications, AE assessment, review of systems, ECOG PS, dosing information, and safety follow-up.

Mobile healthcare - Healthcare visits may be performed by a mobile healthcare provider at locations other than the study site when participants cannot travel to the site due to an exceptional circumstance if written approval is provided by the sponsor. Procedures performed at such visits include, but are not limited to, review of concomitant medications, AE assessment, hospitalization, ECOG PS, dosing information, physical examination, vital signs, ECGs, blood draws, pregnancy tests, urinalysis, and safety follow-up.

Other local healthcare facilities - Procedures that may be done at an alternative location include, but are not limited to, review of concomitant medications, AE assessment, hospitalization, ECOG PS, dosing information, physical examination, vital signs, ECGs, blood draws, pregnancy tests, urinalysis, bone marrow aspirate and biopsy, imaging, and safety follow-up.

*Data capture*

In source documents and the CRF, the study site should capture the visit method, with a specific explanation for any data missing because of missed in-person site visits.

*Safety reporting*

Regardless of the type of remote visits implemented, the protocol requirements regarding the reporting of AEs, SAEs, and PCs remain unchanged.

*Return to on-site visits*

Every effort should be made to enable participants to return to on-site visits as soon as reasonably possible, while ensuring the safety of both the participants and the site staff.

***Local laboratory testing option***

Local laboratory testing may be conducted in lieu of central laboratory testing.

PK collections on C4D1 are optional.

The local laboratory must be qualified in accordance with applicable local regulations.

***Study intervention and ancillary supplies (including participant diaries)***

When a participant is unable to go to the site to receive study supplies during normal on-site visits, the site should work with the sponsor to determine appropriate actions. These actions may include

- asking the participant to go to the site and receive study supplies from site staff without completion of a full study visit
- asking the participant's designee to go to the site and receive study supplies on a participant's behalf, or
- arranging delivery of study supplies.

These requirements must be met before action is taken:

- Alternate delivery of study intervention should be performed in a manner ensures product integrity. The existing protocol requirements for product accountability remain unchanged, including verification of participant's receipt of study supplies.
- When delivering supplies to a location other than the study site (for example, participant's home), the investigator or sponsor, or both, should ensure oversight of the shipping process to ensure accountability and product quality, that is, storage conditions maintained and intact packaging upon receipt.
- Instructions may be provided to the participant or designee on the final disposition of any unused or completed study supplies.

**Documentation**

***Changes to study conduct will be documented***

Sites will identify and document the details of how participants, visit types, and conducted activities were affected by exceptional circumstances. Dispensing or shipment records of study intervention and relevant communications, including delegation, should be filed with site study records.

***Source documents at alternate locations***

Source documents generated at a location other than the study site should be part of the investigator's source documentation and should be transferred to the site in a secure and timely manner.

## 10.8. Appendix 8: Examples of Excluded Medications

The listed medications in this section are commonly used in clinical practice, but the list should not be considered exhaustive. If a medication belonging to one of these drug classes is not included in this table and not mentioned in the table footnotes, then its approved product label should be consulted to determine whether it may be associated with one or more of these drug-drug interaction risks. If so, such medication should also be excluded from coadministration with pirtobrutinib in the clinical trial.

Additional information can be obtained by consulting the pirtobrutinib medical team.

The following table summarizes the drug-drug interaction risk, drug class, and examples of commonly used oral medications in that drug class that should not be coadministered with pirtobrutinib.

| Drug-Drug Interaction Risk | Drug Class | Examples of Medications in Drug Class |
|---|---|---|
| Strong CYP3A inhibitors | Antifungal | Itraconazole<br>Posaconazole<br>Voriconazole[a] |
| | Antiretroviral | Ritonavir<br>Nelfinavir<br>Saquinavir |
| | Kinase inhibitor | Ceritinib<br>Imatinib<br>Nilotinib<br>Ribociclib |
| | Macrolide antibiotic | Clarithromycin<br>Erythromycin<br>Telithromycin[b] |
| | PK booster | Cobicistat |
| Strong CYP3A inducers | Antimicrobial | Rifampin<br>Rifapentine<br>Rifabutin |
| | Androgen receptor inhibitor | Apalutamide<br>Bicalutamide<br>Enzalutamide |
| | Anticonvulsant | Carbamazepine<br>Phenytoin<br>Phenobarbital |
| | OTC supplement | St. John’s wort |
| Sensitive P-gp substrates | Digitalis glycoside | Digoxin |
| | Immunosuppressant | Everolimus<br>Sirolimus<br>Tacrolimus<br>Cyclosporine |
| | Antimalarial | Quinine<br>Quinidine |
| | Antimitotic | Colchicine |
| Sensitive BCRP substrates | Antiadrenergic | Prazosin |
| | Immunosuppressant | High dose methotrexate[c] |

[a] Per protocol exclusion criteria, potential study participants taking oral itraconazole, voriconazole, posaconazole, or ketoconazole should discontinue these medications at least 2 weeks before screening. If the participant is unable to discontinue their antifungal treatment, one of the following alternatives may be substituted at least 2 weeks before screening: oral miconazole, clotrimazole, or fluconazole.

[b] Potential study participants should discontinue erythromycin, clarithromycin, or telithromycin at least 2 weeks before screening. If the participant is unable to discontinue the treatment, they may substitute with azithromycin at least 2 weeks before screening.

[c] Low-dose methotrexate can be considered on a case-by-case basis in consultation with medical practitioners.

## 10.9. Appendix 9: Abbreviations and Definitions

| Term | Definition |
|---|---|
| **abuse** | use of a study intervention for recreational purposes or to maintain an addiction or dependence |
| **AC** | assessment committee |
| **AE** | adverse event |
| **ALP** | alkaline phosphatase |
| **ALT** | alanine aminotransferase |
| **anti-HBc** | hepatitis B core total antibody |
| **AST** | aspartate aminotransferase |
| **authorized IMP** | *Applicable to the EU only*: 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 labeling of the medicinal product, which is used as an investigational medicinal product |
| **authorized AxMP** | *Applicable to the EU only*: 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 labeling of the medicinal product, which is used as an auxiliary medicinal product |
| **AxMP** | auxiliary medicinal product. See also NIMP.<br>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 |
| **BCL2** | B-cell leukemia/lymphoma 2 protein |
| **BCRP** | Breast Cancer Resistance Protein |
| **BOR** | best overall response |
| **BTK** | Bruton tyrosine kinase |
| **C1D1** | cycle 1 day 1 |
| **CFR** | Code of Federal Regulations |
| **CI** | confidence interval |
| **CIOMS** | Council for International Organizations of Medical Sciences |
| **CK** | creatine kinase |

| Term | Definition |
|---|---|
| **CLL** | chronic lymphocytic leukemia |
| **CMV** | cytomegalovirus |
| **complaint** | A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system. |
| **compliance** | Adherence to all study-related, good clinical practice (GCP), and applicable regulatory requirements. |
| **CONSORT** | Consolidated Standards of Reporting Trials |
| **COPD** | Chronic Obstructive Pulmonary Disease |
| **CR** | complete remission |
| **CRi** | complete remission with incomplete hematologic recovery |
| **CRF** | case report form; a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor for each trial participant. |
| **CT** | computed tomography |
| **CTCAE** | Common Terminology Criteria for Adverse Events |
| **CYP3A** | Cytochrome P450 3A enzyme |
| **DOR** | duration of response |
| **ECG** | electrocardiogram |
| **ECOG PS** | Eastern Cooperative Oncology Group Performance Status |
| **EDC** | electronic data capture system |
| **ERB** | Ethical Review Board |
| **enroll** | The act of assigning a participant to a treatment. Participants who are enrolled in the study are those who have been assigned to a treatment. |
| **enter** | Participants entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives. |
| **FISH** | fluorescence in situ hybridization |
| **GCP** | good clinical practice |
| **GGT** | Gamma-glutamyl transferase |
| **HBsAg** | hepatitis B surface antigen |

| Term | Definition |
|---|---|
| **HBV** | hepatitis B virus |
| **HCV** | hepatitis C virus |
| **IB** | Investigator's Brochure |
| **IEC** | Independent Ethics Committees |
| **ICF** | informed consent form |
| **ICH** | International Council for Harmonisation |
| **IGHV** | Immunoglobulin heavy chain variable region gene |
| **IMP** | Investigational Medicinal Product (see also "investigational product")<br>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 participant voluntarily confirms their willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the participant's decision to participate. Informed consent is documented by means of a written, signed, and dated informed consent form. |
| **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 trial, 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. See also "IMP." |
| **IRB** | Institutional Review Boards |
| **IRC** | Independent Review Committee |
| **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 participant (that is, the planned treatment regimen) rather than the actual treatment given. It has the consequence that participant 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. |
| **IWRS** | interactive web-response system |
| **LVEF** | left ventricular ejection fraction |
| **MCL** | Mantle cell lymphoma |

| Term | Definition |
|---|---|
| **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 1 or more of the 5 "rights" of medication use: the right participant, the right drug, the right dose, right route, at the right time.<br>In addition to the core 5 rights, the following may also represent medication errors:<br>• dose omission associated with an AE or a product complaint<br>• dispensing or use of expired medication<br>• use of medication past the recommended in-use date<br>• dispensing or use of an improperly stored medication<br>• use of an adulterated dosage form or administration technique inconsistent with the medication's labeling, for example, Summary of Product Characteristics, IB, local label, and protocol, or<br>• 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. |
| **MRI** | magnetic resonance imaging |
| **NHL** | non-Hodgkin's lymphoma |
| **NIMP** | Non-investigational medicinal product. See AxMP.<br>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. |
| **nPR** | nodular partial response |
| **ORR** | overall response rate |
| **OS** | overall survival |
| **participant** | Equivalent to CDISC term "subject": an individual who participates in a clinical trial, either as recipient of an investigational medicinal product or as a control. |
| **P-gp** | permeability glycoprotein |
| **PI3K- δ** | phosphatidylinositol 3-kinase-delta |
| **PC** | product complaint |
| **PCR** | polymerase chain reaction |
| **PFS** | progression-free survival |
| **PK/PD** | pharmacokinetics/pharmacodynamics |

| Term | Definition |
|---|---|
| **PR** | partial response |
| **QD** | once daily |
| **SAE** | serious adverse event |
| **SAP** | statistical analysis plan |
| **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. |
| **SLL** | small lymphocytic lymphoma |
| **SUSAR** | suspected unexpected serious adverse reactions<br>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. |
| **TBL** | total bilirubin |
| **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. |

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