Protocol: J2N-MC-JZNW (a)

A Phase 1, Open-Label, Drug Interaction Study to Investigate the Effect of Single and Multiple Doses of Pirtobrutinib on the Pharmacokinetics of Rosuvastatin in Healthy Participants

NCT05176314

Approval Date: 22-Dec-2021

Title Page

Protocol Title:

A Phase 1, Open-Label, Drug Interaction Study to Investigate the Effect of Single and Multiple Doses of Pirtobrutinib on the Pharmacokinetics of Rosuvastatin in Healthy Participants

Protocol Number: J2N-MC-JZNW

Amendment Number: (a)

Compound: Pirtobrutinib (LY3527727)

Brief Title:

A drug interaction study investigating the effect of pirtobrutinib on the pharmacokinetics of rosuvastatin.

Study Phase: 1

Sponsor Name: Eli Lilly and Company on behalf of Loxo Onocolgy, Inc., a wholly owned subsidiary of Eli Lilly and Company

Legal Registered Address: Indianapolis, Indiana 46285, USA

Regulatory Agency Identifier Number(s)

IND: 139876

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

Approval Date: 22-Dec-2021 GMT

Medical Monitor Name and Contact Information will be provided separately.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Original Protocol	22-Oct-2021

Amendment (a)

This amendment is considered to be non-substantial.

Overall Rationale for the Amendment:

Section # and Name	Description of Change	Brief Rationale
1.3. Schedule of Activities (SoA)	Added footnote 'g' describing the allowed sampling windows for pirtobrutinib and rosuvastatin PK.	To provide clarification to the site and for consistency with the database.
4.1. Overall Design	Removed 'single-site' from the description of the study.	A second site has been added to conduct the study and therefore 'single-site' no longer applies.
5.2. Exclusion Criteria	Updated exclusion criterion #19 to clarify that participants must be willing to stop alcohol consumption for 48 hours (rather than 24 hours) prior to admission.	Minor change to clarify an inconsistency in the original protocol.
6.1.1. Administration Details	Added language to instruct that pirtobrutinib be dosed at the same time as rosuvastatin or no more than 15 minutes beforehand.	To provide clarification to the site.

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1. Protocol Summary

1.1. Synopsis

Protocol Title:

A Phase 1, Open-Label, Drug Interaction Study to Investigate the Effect of Single and Multiple Doses of Pirtobrutinib on the Pharmacokinetics of Rosuvastatin in Healthy Participants

Brief Title:

A drug interaction study investigating the effect of pirtobrutinib on the pharmacokinetics of rosuvastatin.

Rationale:

The breast cancer resistance protein (BCRP) is a membrane-bound transporter located in the gastrointestinal tract, liver, kidney, brain endothelium, mammary tissue, testis, and placenta, responsible for exporting a wide range of substrates across biological membranes. Certain substrates of BCRP have been shown to have clinically significant drug interactions when administered with inhibitors of BCRP.

Rosuvastatin is a commonly used index substrate for BCRP (FDA, 2021). Pirtobrutinib is an inhibitor of BCRP in vitro. Therefore, this study aims to investigate a potential drug-drug interaction by evaluating the pharmacokinetics (PK), safety, and tolerability of rosuvastatin in the presence of pirtobrutinib.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To evaluate the effect of single and multiple doses of pirtobrutinib on BCRP activity in healthy participants	• C_{max} and AUC(0-∞) of rosuvastatin
Secondary	
• To evaluate the safety and tolerability of rosuvastatin in combination with pirtobrutinib in healthy participants.	• Incidence of TEAEs and SAEs

Abbreviations: AUC(0-∞) = area under the concentration versus time curve from time zero to infinity; BCRP = breast cancer resistance protein; C_{max} = maximum observed drug concentration; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

Overall Design

Brief Summary:

Study J2N-MC-JZNW (JZNW) is a Phase 1, open-label, drug interaction study evaluating the effect of single and multiple doses of pirtobrutinib on the PK, safety, and tolerability of rosuvastatin.

Number of Participants:

Approximately 36 participants will be enrolled to ensure that at least 28 evaluable participants complete the study**.**

Intervention Groups and Duration:

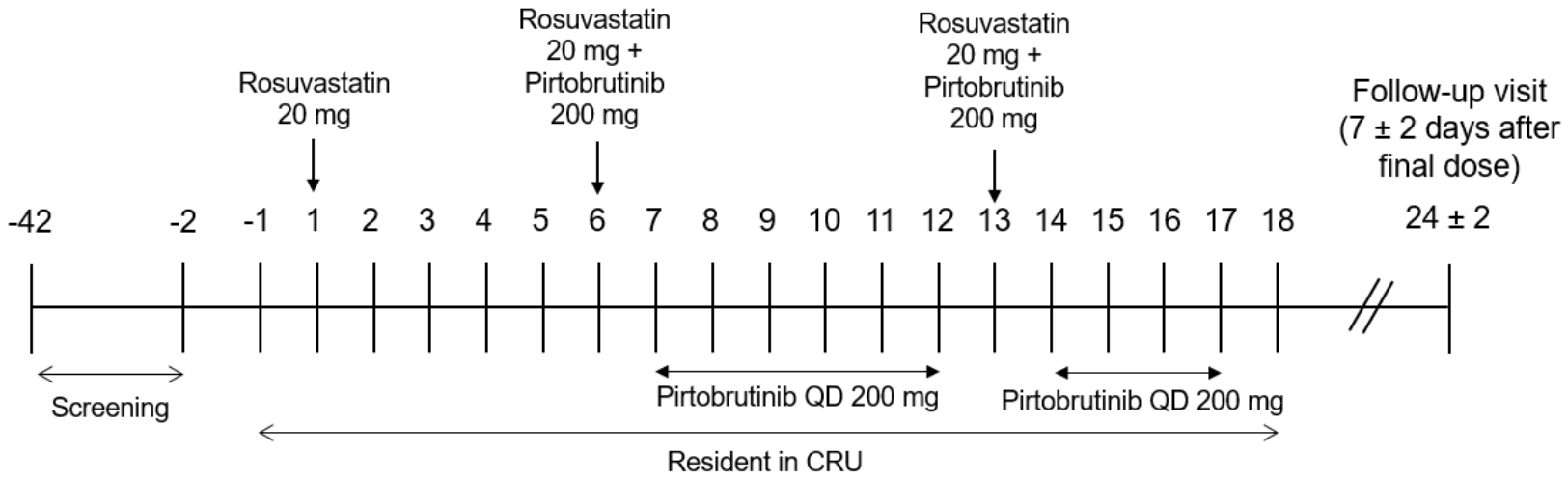
All participants will be screened within 42 days prior to enrollment. Eligible participants will be admitted to the clinical research unit (CRU) on Day -1 and remain resident in the CRU until discharge on Day 18. A follow-up visit will be performed 7 (± 2) days after the last dose of study intervention.

Participants will receive the following study intervention while resident in the CRU:

- Day 1: 20 mg rosuvastatin alone
- Day 6: 20 mg rosuvastatin co-administered with 200 mg pirtobrutinib
- Days 7 to 12: once daily (QD) doses of 200 mg pirtobrutinib alone
- Day 13: 20 mg rosuvastatin co-administered with 200 mg pirtobrutinib
- Days 14 to 17: QD doses of 200 mg pirtobrutinib alone.

Data Monitoring Committee: No

1.2. Schema



Abbreviations: CRU = clinical research unit; QD = once daily.

1.3. Schedule of Activities (SoA)

Study Procedure	Screening (D-42 to -2)	Treatment Period (Study Days)																		FU/ ED[b]
		-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18[a]	24 (± 2 days)
Informed consent	X																				
Admission to CRU		X																			
Discharge from CRU																				X	
Outpatient visit	X																				X
Medical history and demographics	X																				
Participant eligibility	X	X																			
Rosuvastatin administration			X					X							X						
Pirtobrutinib administration								X	X	X	X	X	X	X	X	X	X	X	X		
Height	X																				
Weight	X																				
Pregnancy test[c]	X	X																		X	
Urine drug screen (including cotinine)	X	X																			
Ethanol test		X																			
Supine vital signs (PR and BP)[d]	X		P, 2 h	24 h				P, 2 h	24 h						P, 2 h	24 h				X	X
Oral body temperature	X																				

Study Procedure	Screening (D-42 to -2)	Treatment Period (Study Days)																		FU/ ED[b]
		-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18[a]	24 (± 2 days)
12-lead ECG	X		P		X			P		X					P		X			X	X
Clinical laboratory tests	X		P		X			P		X					P		X			X	X
Physical examination[e]		X																		X	X
Genetic blood sample for screening	X																				
CCI																					
Rosuvastatin PK samples[g]			P, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12 h	24 h	48 h	72 h	96 h	Pf, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12 h	24 h	48 h	72 h	96 h	120 h		P, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12 h	24 h	48 h	72 h	96 h	120 h	
CCI																					
Adverse event review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: BP = blood pressure; CRU = clinical research unit; D = day; ECG = electrocardiogram; ED = early discontinuation; FU = follow-up; h = hours postdose; P = predose; PK = pharmacokinetic(s); PR = pulse rate.

[a] Participants will be discharged from the CRU on Day 18 once all study procedures are completed.

[b] Participants will attend an outpatient follow-up visit 7 (± 2) days after the final dose of study intervention. If participants are not able to attend the CRU for this visit, the CRU should contact the participant via phone call to conduct adverse event and concomitant medication review. If applicable, ED assessments should be performed on the day of discontinuation (or as close to it as possible).

[c] Female participants only. Serum pregnancy test at screening and urine pregnancy test at all other times.

CCI

[e] Complete physical examination at check-in, discharge from CRU, and follow-up. Additional symptom-driven physical examinations may be performed at the discretion of the investigator.

CCI

2. Introduction

2.1. Study Rationale

The breast cancer resistance protein (BCRP) is a membrane-bound transporter located in the gastrointestinal tract, liver, kidney, brain endothelium, mammary tissue, testis, and placenta, responsible for exporting a wide range of substrates across biological membranes. Certain substrates of BCRP have been shown to have clinically significant drug interactions when administered with inhibitors of BCRP (International Transporter Consortium et al. 2010).

Rosuvastatin is a commonly used index substrate for BCRP (FDA, 2021). Pirtobrutinib is an inhibitor of BCRP in vitro, with a half maximal inhibitory concentration of 18 μM. Therefore, this study aims to investigate a potential drug-drug interaction (DDI) by evaluating the pharmacokinetics (PK), safety, and tolerability of rosuvastatin in the presence of pirtobrutinib.

2.2. Background

Pirtobrutinib is a selective inhibitor of the Bruton's tyrosine kinase (BTK). BTK is a key component of the B-cell receptor signaling complex and plays a critical role in the proliferation and survival of diverse B cell malignancies. Pirtobrutinib is a small molecule designed to block the adenosine triphosphate binding site of the BTK kinase competitively.

Pirtobrutinib is currently being studied in an ongoing first-in-human study (LOXO-BTK-18001), in patients with previously treated chronic lymphocytic leukemia/small lymphocytic leukemia, or non-Hodgkin's lymphoma. Pirtobrutinib is also being studied in three Phase 3 studies in patients with hematological malignancies. In addition, pirtobrutinib has been investigated in twelve Phase 1 studies in healthy participants and participants with renal impairment. One of these studies in participants with hepatic impairment and matched healthy controls is ongoing.

As of a data cutoff date of September 27, 2020, safety data were available from a total of 324 patients treated in Study LOXO-BTK-18001, with monotherapy doses ranging from 25 to 300 mg once daily (QD).

From the available safety data across the 324 patients in the first-in-human study (LOXO-BTK-18001):

- the treatment-emergent adverse events (TEAEs) reported in ≥10% of patients were
  - fatigue (20.1% total, 8.3% considered related to study drug)
  - diarrhea (17.0% total, 8.6% considered related to study drug)
  - contusion (13.0% total, 9.0% considered related to study drug).
- TEAEs considered related to study drug were reported in 156 of 324 patients (48.1%)
- TEAEs of severity Grade 3 or 4 were reported in 87 of 324 patients (26.9%), with 41 (12.7%) of these Grade 3 or 4 TEAEs reported as related to study drug
- On-study death (death within 28 days of the last dose of study drug) due to a Grade 5 (fatal) adverse event (AE) was reported in 4 of 324 patients (1.2%)

- One Grade 5 AE, *Enterococcus faecium*-related septic shock, was considered related to study drug. All other Grade 5 AEs were considered to be not related to study drug; these included pneumonia fungal, shock, and pleural effusion.

Across the Phase 1 studies, pirtobrutinib has been administered to a total of 184 healthy participants (at the time of this protocol's development) at single doses from 200 to 900 mg and multiple doses of 200 mg for a maximum of 14 days.

From the available safety data in Phase 1 studies, treatment-related TEAEs have been reported in 30 (16%) healthy participants. The most frequently reported treatment-related TEAEs were petechiae and headache. The majority of treatment-related TEAEs were Grade 1 (mild) in severity and all AEs had resolved by the end of study.

As part of each clinical study conducted in patients or healthy participants, electrocardiogram (ECG) and vital signs are performed at intervals specified by the protocol. For study LOXO-BTK-18001 conducted in patients, no clinically significant findings of corrected QT interval (QTc) prolongation have been identified in the 330 patients as of September 27, 2020. In addition, there have been no clinically significant abnormal findings in vital signs and ECG data in the studies investigating pirtobrutinib conducted in healthy participants to date.

Preliminary data after oral administration of single doses of pirtobrutinib ranging from 25 to 300 mg QD suggest the median time to maximum drug concentration (t_{max}) is approximately 2 hours, the terminal half-life ($t_{1/2}$) is approximately 20 hours, and the PK is dose proportional.

2.3. Benefit/Risk Assessment

The 200 mg QD dose of pirtobrutinib administered in this study is not anticipated to induce any potential risk to participants as the dose does not exceed the highest dose safely administered in the clinical studies in patients or healthy participants. This dose and dosing regimen were selected as they represent the recommended phase 2 dose (RP2D) based on the PK, safety, and antitumor activity observed in the Phase 1/2 study (Study LOXO-BTK-18001). In patients, pirtobrutinib has demonstrated a safe and tolerable profile across all doses tested (25 to 300 mg QD). No dose-limiting toxicities occurred in Study LOXO-BTK-18001, and no maximum tolerated dose was identified. No clinically significant safety or tolerability concerns have been identified in healthy participants to date for pirtobrutinib up to the highest single dose of 900 mg and multiple doses of 200 mg for up to 14 days.

There is no anticipated therapeutic benefit for the participants in this study. However, participants may benefit from the screening procedures (through detection of unknown health issues) even if they receive no therapeutic benefit from the study.

More detailed information about the known and expected benefits and risks of pirtobrutinib may be found in the Investigator's Brochure.

Rosuvastatin is a commonly used drug in DDI studies and the dosing regimen in the current study (20 mg) is consistent with the prescribing recommendations. The most frequent (≥2%) adverse reactions following rosuvastatin dosing are headache, myalgia, abdominal pain, asthenia, and nausea. Cases of myopathy and rhabdomyolysis have been reported with rosuvastatin. These risks can occur at any dose level, but are increased at the highest dose of 40 mg. The incidence of rhabdomyolysis is 0.3 to 13.5 cases per 1,000,000 (Mendes et al. 2014). During the current

study, participants should promptly report any unexplained muscle pain, tenderness, or weakness. Elevations in liver enzymes (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) have been reported following rosuvastatin dosing. In most cases, the elevations were transient and resolved or improved on continued dosing or after brief interruption of dosing. In the current study, blood samples to determine liver enzymes (as part of clinical laboratory tests) will be collected prior to each dosing occasion of rosuvastatin.

More detailed information about the known and expected benefits and risk of rosuvastatin may be found in the prescribing information (Crestor® Prescribing Information, 2020).

3. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the effect of single and multiple doses of pirtobrutinib on BCRP activity in healthy participants	• C_{max} and AUC(0-∞) of rosuvastatin
Secondary	
• To evaluate the safety and tolerability of rosuvastatin in combination with pirtobrutinib in healthy participants	• Incidence of TEAEs and SAEs

Abbreviations: AUC(0-∞) = area under the concentration versus time curve from time zero to infinity; BCRP = breast cancer resistance protein; C_{max} = maximum observed drug concentration; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

4. Study Design

4.1. Overall Design

Study J2N-MC-JZNW is a Phase 1, fixed sequence, open-label study in healthy participants that will investigate the effect of single and multiple doses of pirtobrutinib on the PK of rosuvastatin.

The schema in Section 1.2 illustrates the study design.

Approximately 36 participants will be enrolled to ensure that at least 28 evaluable participants complete the study.

Screening

All participants will be screened for study inclusion within 42 days prior to enrollment (Day 1). Screening should not occur less than 14 days prior to enrollment (Day 1), in order to allow sufficient time to receive genotyping results.

Treatment and Assessment Period

Participants will check in to the clinical research unit (CRU) on Day -1 and remain resident until discharge on Day 18.

While resident at the CRU, all participants will receive study intervention as follows:

- Day 1: 20 mg rosuvastatin alone
- Day 6: 20 mg rosuvastatin co-administered with 200 mg pirtobrutinib
- Days 7 to 12: QD doses of 200 mg pirtobrutinib alone
- Day 13: 20 mg rosuvastatin co-administered with 200 mg pirtobrutinib
- Days 14 to 17: QD doses of 200 mg pirtobrutinib alone.

PK blood sampling and safety assessments, including vital signs measurements, physical examinations, clinical laboratory tests, ECGs, and AE recording, will be performed according to the Schedule of Activities (SoA; Section 1.3).

Participants will be discharged from the CRU on Day 18 following completion of study procedures, provided they are deemed medically fit by the investigator or designee.

Follow-Up

Participants will attend an outpatient follow-up visit 7 (± 2) days after the final dose of study intervention. If participants are not able to attend the CRU for this visit, the CRU should contact the participant via phone call to conduct AE and concomitant medication review.

4.2. Scientific Rationale for Study Design

In order to allow each subject to act as their own control for safety and PK comparisons, a fixed sequence design has been selected.

This study will be open label as the study primary endpoint PK measures are objective rather than subjective.

Based on the $t_{1/2}$ of rosuvastatin (19 hours; Crestor® Prescribing Information, 2020), a period of 4 to 5 days between rosuvastatin doses is considered sufficient time for the study intervention to washout. Based on the PK profile of pirtobrutinib, QD dosing for 7 days is considered sufficient time for pirtobrutinib to reach steady state.

The PK of rosuvastatin will be evaluated after a single pirtobrutinib dose on Day 6 to assess the effect on intestinal BCRP and after multiple pirtobrutinib doses on Day 13 to assess the effect on systemic BCRP.

Conducting the study in healthy participants mitigates the potential confounding effects of the disease state, other medical conditions, and concomitant medications in patients.

4.3. Justification for Dose

Pirtobrutinib 200 mg QD is the chosen recommended Phase 2 dose for the ongoing global Phase 1/2 first-in-human study (LOXO-BTK-18001) in patients previously treated for chronic lymphocytic leukemia/small lymphocytic leukemia or non-Hodgkin's lymphoma. Previous clinical data in healthy participants demonstrate that pirtobrutinib is safe and well tolerated at doses of 200 mg QD with no dose-limiting toxicities identified in humans.

Rosuvastatin is a commonly used drug in DDI studies. The dosing regimen of rosuvastatin (20 mg) in the current study is consistent with the prescribing recommendations.

4.4. End of Study Definition

The end of the study is defined as the date of the last scheduled procedure shown in the SoA (Section 1.3) for the last participant in the study.

A participant is considered to have completed the study if the participant has completed the treatment period of the study and follow-up procedures as shown in the SoA (Section 1.3).

5. Study Population

Eligibility of participants for enrollment in the study will be based on the results of screening medical history, vital signs, clinical laboratory tests, and ECG, and physical examination at check-in (Day -1). The nature of any conditions present at the time of the physical examination and any pre-existing conditions will be documented.

Screening may occur up to 42 days prior to enrollment. Eligible participants who are not enrolled within 42 days of screening may undergo an additional medical assessment and/or clinical measurements to confirm their eligibility. In such instances, repeat the following tests and procedures: weight, vital signs, ECG, clinical laboratory tests, physical examination, and pregnancy test (females only). Any other procedures may be repeated at the discretion of the investigator.

The inclusion and exclusion criteria used to determine eligibility should be applied at screening only, unless otherwise specified, 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:

Participant Characteristics

1. Are males, or females not of childbearing potential
    a. Reproductive definitions and contraception requirements are provided in Appendix 4 (Section 10.4).
2. Are between 18 and 64 years of age inclusive, at the time of signing the informed consent.
3. Have a body mass index of 18.0 to 32.0 kg/m^2 (inclusive) and a body weight of at least 50 kg.
4. Are overtly healthy as determined by medical evaluation including medical history, physical examination (at check-in/Day -1), vital signs, and ECG.
5. Have clinical laboratory test results within normal reference range for the population or investigative site, or results with acceptable deviations that are judged to be not clinically significant by the investigator, except for the following parameters which must be within the specified ranges:
    a. ALT and AST ≤1.5 × upper limit of normal (ULN)
    b. Total bilirubin (TBL) ≤1.5 × ULN (isolated bilirubin >1.5 × ULN is acceptable if TBL is fractionated and direct bilirubin is <35%).
6. Have venous access sufficient to allow for blood sampling as per protocol.

Informed Consent

7. Capable of giving signed informed consent as described in Appendix 1 (Section 10.1), which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

5.2. Exclusion Criteria

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

Medical Conditions

1. Have known allergies to pirtobrutinib or rosuvastatin, related compounds, or any components of the formulation.
2. Have an abnormal blood pressure and/or pulse rate, deemed to be clinically significant by the investigator.
3. Have a significant history of or current cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine, hematological, neurological, or psychiatric disorder or surgery (including cholecystectomy) capable of significantly altering the absorption, metabolism, or elimination of drugs; of constituting a risk when taking the investigational product; or of interfering with the interpretation of data.
    a. Note: history of uncomplicated appendectomy will be allowed.
4. Have had lymphoma, leukemia, or any malignancy within the past 5 years except for basal cell or squamous epithelial carcinomas of the skin that have been resected with no evidence of metastatic disease for 3 years.

Prior/Concomitant Therapy

5. Have used or intend to use prescription or nonprescription medication (including dietary supplements, vitamins, and/or herbal medications), or modulators of CYP3A4 or BCRP within 7 days prior to dosing, unless, in the opinion of the investigator and sponsor, the medication will not interfere with the study.
6. Vaccination with live vaccines within 28 days prior to screening, or plans to receive such vaccines during the study.
    a. Note: use of non-live (inactivated) vaccinations will be allowed.

Prior/Concurrent Clinical Study Experience

7. Are currently enrolled in any other clinical study involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study.
8. Have participated, within the last 30 days, in a clinical study involving an investigational product. If the previous investigational product has a long half-life, 5 half-lives or 30 days (whichever is longer) should have passed.
9. Have previously completed or withdrawn from this study or any other study investigating pirtobrutinib (also known as LOXO-305).

Diagnostic Assessments

10. Show evidence of human immunodeficiency virus (HIV) infection and/or positive human HIV antibodies.
11. Show evidence of hepatitis C and/or positive hepatitis C antibody.
12. Show evidence of hepatitis B and/or positive hepatitis B surface antigen.

Other Exclusions

13. Have c.34AA, c.421AA, or c.34GA/421CA genotypes of ABCG2 as determined through genotyping.
14. Have c.521TC and c/521CC genotypes of SLCO1B1 as determined by genotyping.
15. Are females who are lactating or have a positive pregnancy test.
16. Regularly use known drugs of abuse or show positive findings on drug screening.
17. Have donated blood of more than 500 mL within the previous 3 months of study screening.
18. Have an average weekly alcohol intake that exceeds 21 units per week (males) and 14 units per week (females). If calculation of units is required, use the following equation: Number of units = [total volume of drink (mL) × ABV (%)]/1000, where ABV is alcohol by volume.
19. Are unwilling to stop alcohol consumption 48 hours prior to admission and while resident at the CRU.
20. Use of tobacco- or nicotine-containing products within 1 month prior to check-in, or positive cotinine test at screening or check-in.
21. Are investigative site personnel directly affiliated with this study and/or their immediate families. Immediate family is defined as a spouse, biological or legal guardian, child, or sibling.
22. Are Lilly or Labcorp employees.
23. In the opinion of the investigator or sponsor, are unsuitable for inclusion in the study.

5.2.1. Rationale for Exclusion of Certain Study Participants

The human BCRP transporter (also known as ABCG2) is polymorphic. Participants with the c.34AA, c.421AA, and c.34GA/421CA genotypes will be excluded because these genetic polymorphisms are associated with impaired BCRP activity (Furukawa et al. 2009, Wan et al. 2015, Keskitalo et al. 2009). Because the activity of BCRP is impaired with these participants, it would be anticipated that even complete inhibition of BCRP would not result in a substantial change in rosuvastatin exposure. Accordingly, excluding participants with these polymorphisms will ensure that the "worst-case" interaction between pirtobrutinib and rosuvastatin will be evaluated in this study.

The human OATP1B1 transporter (also known as SLCO1B1) is also polymorphic. In order to evaluate worst-case interactions between pirtobrutinib and rosuvastatin, participants with the c.521TC and c/521CC genotypes will be excluded from this study because this genetic polymorphism is associated with decreased transporting activity of OATP1B1 (Niemi et al. 2011) and higher plasma rosuvastatin concentrations (Crestor® Prescribing Information, 2020).

5.3. Lifestyle Considerations

Throughout the study, participants may undergo medical assessments and review of compliance with requirements before continuing in the study.

5.3.1. Meals and Dietary Restrictions

While resident in the CRU, participants will consume only food and beverages that are provided to them by the CRU staff. Standard meals (breakfast, lunch, dinner, and snack) will be provided to the participants while resident at the CRU.

Rosuvastatin and pirtobrutinib will be administered after an overnight fast of at least 8 hours on Days 1, 6, and 13. On these days, participants will remain fasted for approximately 4 hours postdose, at which time a meal will be served. Water is permitted ad libitum during the fasting period, except for 1 hour before and after dose administration (other than the water provided during dosing). On all other dosing days (i.e., pirtobrutinib alone on Days 7 to 12 and 14 to 17), there are no fasting requirements for dosing.

Participants will refrain from consumption of grapefruit or grapefruit juice from 7 days before the start of study intervention until after the final PK sample collection.

5.3.2. Substance Use: Caffeine, Alcohol, and Tobacco

Participants will abstain from ingesting caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks, and chocolate) for 48 hours prior to check-in until discharge from the CRU.

Participants will abstain from alcohol for 48 hours prior to check-in until discharge from the CRU.

Participants will not be permitted to use tobacco- or nicotine-containing products within 1 month prior to check-in until the follow-up visit.

5.3.3. Activity

Participants will abstain from strenuous exercise for 48 hours before each blood collection for clinical laboratory tests. Participants may participate in light recreational activities during the study (e.g., watching television, reading).

5.4. Screen Failures

A screen failure occurs when a participant who consents to participate in the clinical study is not subsequently enrolled in the study.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. There must be at least 2 weeks between the screen failure and the new screening. Rescreened participants should be assigned a new participant number for the rescreening event.

If applicable, participants may be re-tested up to 1 time at the discretion of the investigator (e.g., abnormal laboratory result) before being deemed a screen failure.

Eligible participants who are not enrolled within 42 days of screening may undergo an additional medical assessment and/or clinical measurements to confirm their eligibility; see Section 5 for a list of required assessments in these cases.

6. Study Interventions and Concomitant Therapy

Study intervention is defined as any investigational intervention(s) or marketed product(s), intended to be administered to/used by a study participant according to the study protocol.

6.1. Study Interventions Administered

This study involves the comparison of rosuvastatin administered alone and rosuvastatin co-administered with pirtobrutinib. Table JZNW.1 shows the study interventions to be administered.

Table JZNW.1 Study Interventions Administered

Study Intervention	Rosuvastatin	Pirtobrutinib
Dosage Formulation	Tablet	Tablet
Unit Dose Strength/Dosage Level	2 × 10-mg tablets (20-mg dose)	2 × 100-mg tablets (200-mg dose)
Route of Administration	Oral	Oral
Dosing Instructions	2 tablets administered alone on Day 1 and with pirtobrutinib on Days 6 and 13	2 tablets administered with rosuvastatin on Days 6 and 13, and alone on Days 7 to 12 and 14 to 17

6.1.1. Administration Details

Each dose of rosuvastatin and pirtobrutinib will be administered orally with approximately 240 mL of room temperature water in the morning of each dosing day (see Section 1.3) in a sitting position. When rosuvastatin and pirtobrutinib are administered concurrently, 240 mL of room temperature water will be used for all tablets and pirtobrutinib should be administered at the same time as rosuvastatin or no more than 15 minutes prior to rosuvastatin. If required to complete dosing, additional water may be given in 50 mL aliquots and will be recorded in the source but will not be considered as a protocol deviation.

Participants will not be allowed to lie supine for 2 hours after dosing, unless clinically indicated or for study procedures.

Doses of rosuvastatin and pirtobrutinib on Days 1, 6, and 13 will be administered after an overnight fast of at least 8 hours and participants will remain fasting for approximately 4 hours postdose. Water is permitted ad libitum during the fasting period, except for 1 hour before and after dose administration. On all other dosing days (i.e., pirtobrutinib alone on Days 7 to 12 and 14 to 17), there are no fasting requirements for dosing.

6.2. Preparation, Handling, Storage, and Accountability

1. 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.

2. 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.
3. The investigator or authorized study personnel are responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
4. The investigator or designee will return all unused study intervention to Lilly or its designee at the end of the study. Note: In some cases, sites may destroy the material if, during the investigative site selection, the evaluator has verified and documented that the site has appropriate facilities and written procedures to dispose of clinical materials.

6.3. Measures to Minimize Bias: Randomization and Blinding

This is a non-randomized, open-label study.

6.4. Study Intervention Compliance

Participants will be dosed at the CRU and they will be administered study intervention under medical supervision by the investigator or designee. The dose of study intervention and study participant identification will be confirmed prior to the time of dosing. The date and time of each dose administered will be recorded in the source documents and in the case report form (CRF).

Study site personnel will examine each participant's mouth to ensure that the study intervention was ingested.

6.5. Dose Modification

Dose modification is not permitted in this study.

6.6. Continued Access to Study Intervention after the End of the Study

Pirtobrutinib or rosuvastatin will not be made available to participants after completion of the study.

6.7. Treatment of Overdose

For this study, any dose of pirtobrutinib greater than 200 mg or rosuvastatin greater than 20 mg within a calendar day will be considered an overdose.

The sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should:

- Contact the Lilly clinical pharmacologist (CP) immediately.
- Closely monitor the participant for any AE/serious adverse event (SAE) and laboratory abnormalities
- Obtain a plasma sample for PK analysis if requested by the Lilly CP (determined on a case-by-case basis).

- Document the quantity of the excess dose in the CRF.

6.8. Concomitant Therapy

Any medication or vaccine (including prescription or nonprescription medication, dietary supplements, vitamins, and/or herbal medications) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency for concomitant therapy of special interest.

The Lilly CP should be contacted if there are any questions regarding concomitant or prior therapy.

Participants must abstain from taking prescription or nonprescription drugs (including dietary supplements, vitamins, and/or herbal medications), or modulators of CYP3A4 or BCRP within 7 days prior to dosing until completion of the follow-up visit, unless, in the opinion of the investigator and sponsor, the medication will not interfere with the study.

Participants will not have received a live vaccine within 28 days prior to screening and will abstain from receiving such vaccines until completion of the follow-up visit.

Acetaminophen is permitted for use at the discretion of the investigator. If acetaminophen treatment is needed for pain management, the maximal allowed dose will be 3 g/day from all acetaminophen-containing medicinal products. Other concomitant medication may be considered on a case-by-case basis by the investigator in consultation with the Lilly CP.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

Participants discontinuing from study intervention or from the study prematurely for any reason should complete AE and other early discontinuation procedures as per the SoA (Section 1.3).

Discontinuation of specific sites or of the study as a whole is described in Appendix 1 (Section 10.1.7).

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention. If study intervention is permanently discontinued, the participant will remain in the study for appropriate safety monitoring. See the SoA (Section 1.3) for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

7.1.1. Hepatic Criteria for Discontinuation

The study intervention should be discontinued if one or more of these conditions occur:

Elevation	Exception
ALT or AST >5× ULN	
ALT or AST >3× ULN and either TBL >2× ULN or INR >1.5	In participants with Gilbert's syndrome, doubling of direct bilirubin should be used for drug interruption or discontinuation decisions rather than TBL >2× ULN.
ALT or AST >3× ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)	
ALP >3× ULN (when the source of increased ALP is the liver)	
ALP >2.5× ULN and TBL > 2× ULN	In participants with Gilbert's syndrome, doubling of direct bilirubin should be used for drug interruption or discontinuation decisions rather than TBL >2× ULN.
ALP >2.5× ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)	

Source: FDA Guidance for Industry: Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009 and other consensus guidelines with minor modifications

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; FDA = Food and Drug Administration; INR = international normalized ratio; TBL = total bilirubin; ULN = upper limit of normal.

Participants who discontinue from study intervention due to the abnormal liver tests will undergo monitoring as described in Appendix 6 (Section 10.6).

7.2. Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the study:

- at any time at the participant's own request
- at the request of the participant's designee (for example, parents or legal guardian)
- at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons
- if enrollment in any other clinical study involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
- if the participant, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication, discontinuation from the study occurs prior to introduction of the new agent.

Discontinuation is expected to be uncommon.

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA (Section 1.3). See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed. The participant will be permanently discontinued from both the study intervention and the study at that time.

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

7.3. Lost to Follow-Up

A participant will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. Site personnel or designee are 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.

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.

The specifications in this protocol for the timings of safety and sample collection are given as targets to be achieved within reasonable limits. Modifications may be made to the time points based upon emerging clinical information. The scheduled time points may be subject to minor alterations; however, the actual time must be correctly recorded in the CRF.

Appendix 2 (Section 10.2) lists the laboratory tests that will be performed for this study.

Appendix 2 (Section 10.2.1) provides a summary of the maximum number and volume of invasive samples, for all sampling, during the study.

Unless otherwise stated in subsections below, all samples collected for specified laboratory tests will be destroyed within 60 days of receipt of confirmed test results. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.

8.1. Efficacy Assessments

Efficacy is not evaluated in this study.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

8.2.1. Physical Examinations

A complete physical examination will be conducted as specified in the SoA (Section 1.3). Complete physical examinations include, at a minimum, assessments of the following systems:

- dermatological
- head and eyes
- ears, nose, mouth, and throat
- pulmonary
- cardiovascular
- abdominal
- lymphatic
- musculoskeletal/extremities
- neurological.

Symptom-directed examinations may be performed as deemed appropriate by investigator.

Any clinically significant findings in a physical examination should be reported as AEs.

8.2.2. Height and Weight

Height and weight will be measured and recorded at screening only (see SoA, Section 1.3).

8.2.3. Vital Signs

For each participant, vital signs measurements should be conducted according to the SoA (Section 1.3).

Blood pressure and pulse rate should be measured after at least 5 minutes in a supine position.

Unscheduled orthostatic vital signs should be assessed, if possible, during any AE of dizziness or posture-induced symptoms. If orthostatic measurements are required, participants should be supine for at least 5 minutes and stand for at least 2 minutes. If the participant feels unable to stand, supine vital signs only will be recorded.

Oral body temperature will be recorded at screening only.

Additional vital signs may be measured if warranted.

8.2.4. Electrocardiograms

For each participant, a single12-lead digital ECG will be collected according to the SoA (Section 1.3). ECGs may be obtained at additional times, when deemed clinically necessary.

If scheduled at the same nominal time, ECGs must be recorded before collecting any blood samples. Participants must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection. All ECGs recorded should be stored at the investigational site.

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

If a clinically significant finding is identified (including, but not limited to, changes in QT/QTc intervals from baseline) after enrollment, the investigator will determine if the participant can continue in the study. The investigator, or qualified designee, is responsible for determining if any change in participant management is needed, and must document his/her review of the ECG printed at the time of collection.

Any new clinically relevant finding should be reported as an AE.

8.2.5. Clinical Laboratory Tests

See Appendix 2 (Section 10.2) for the list of clinical laboratory tests to be performed and the SoA (Section 1.3) 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.

All laboratory tests with values considered clinically significantly abnormal during participation in the study 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 Appendix 2 (Section 10.2), must be conducted in accordance with the SoA (Section 1.3), 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 (e.g., SAE or AE or dose modification), then report the information as an AE.

8.2.6. Pregnancy Testing

Where applicable, pregnancy tests will be performed as outlined in the SoA (Section 1.3).

8.2.7. Safety Monitoring

The Lilly CP or clinical research physician (CRP) will monitor safety data throughout the course of the study.

Lilly will review SAEs within time frames mandated by company procedures. The Lilly CP or CRP will periodically review the following data:

- trends in safety data
- laboratory analytes
- AEs.

When appropriate, the Lilly CP or CRP will consult with the functionally independent Global Patient Safety therapeutic area physician or clinical research scientist.

8.2.7.1. Hepatic Safety

Close hepatic monitoring

Laboratory tests (Appendix 6, Section 10.6), including ALT, AST, alkaline phosphatase (ALP), and TBL, should be repeated, with the addition of direct bilirubin, gamma glutamyl transferase, and creatine kinase, within 48 to 72 hours to confirm the abnormality and to determine if it is increasing or decreasing, if 1 or more of these conditions occur:

If a participant with baseline results of...	develops the following elevations:
ALT or AST <1.5 × ULN	ALT or AST ≥3 × ULN
ALP <1.5 × ULN	ALP ≥2 × ULN

TBL <1.5 × ULN	TBL ≥2 × ULN (except for participants with Gilbert's syndrome)
ALT or AST ≥1.5 × ULN	ALT or AST ≥2 × baseline
ALP ≥1.5 × ULN	ALP ≥2 × baseline
TBL ≥1.5 × ULN	TBL ≥1.5 × baseline (except for participants with Gilbert's syndrome)

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 CP. 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), recent travel, history of concomitant medications (including over-the-counter), herbal and dietary supplements, and history of alcohol drinking and other substance abuse.

Initially, monitoring of symptoms and hepatic biochemical tests should be done at a frequency of 1 to 3 times weekly, based on the participant's clinical condition and hepatic biochemical tests. Subsequently, the frequency of monitoring may be lowered to once every 1 to 2 weeks, if the participant's clinical condition and laboratory results stabilize. Monitoring of ALT, AST, ALP, and TBL should continue until levels normalize or return to approximate baseline levels.

Comprehensive hepatic evaluation

A comprehensive evaluation should be performed to search for possible causes of liver injury if one or more of these conditions occur:

If a participant with baseline results of...	develops the following elevations:
ALT or AST <1.5 × ULN	ALT or AST ≥3 × ULN with hepatic signs/symptoms*, or ALT or AST ≥5 × ULN
ALP <1.5 × ULN	ALP ≥3 × ULN
TBL <1.5 × ULN	TBL ≥2 × ULN (except for participants with Gilbert's syndrome)
ALT or AST ≥1.5 × ULN	ALT or AST ≥2 × baseline with hepatic signs/symptoms*, or ALT or AST ≥3 × baseline
ALP ≥1.5 × ULN	ALP ≥2 × baseline
TBL ≥1.5 × ULN	TBL ≥2 × baseline (except for participants with Gilbert's syndrome)

* Hepatic signs/symptoms are severe fatigue, nausea, vomiting, right upper quadrant abdominal pain, fever, rash, and/or eosinophilia >5%.

At a minimum, this evaluation should include physical examination and a thorough medical history, as outlined above, as well as tests for prothrombin time-international normalized ratio; tests for viral hepatitis A, B, C, or E; tests for autoimmune hepatitis; and an abdominal imaging study (for example, ultrasound or computed tomography scan).

Based on the participant's history and initial results, further testing should be considered in consultation with the Lilly-designated CP, 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 serum

phosphatidylethanol. 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 data collection in study participants who have abnormal liver test results during the study

Additional hepatic safety data collection in hepatic safety CRF should be performed in study participants who meet 1 or more of the following conditions:

- Elevation of serum ALT to ≥5 × ULN on 2 or more consecutive blood tests (if baseline ALT <1.5× ULN)
    - In participants with baseline ALT ≥1.5 × ULN, the threshold is ALT ≥3 × baseline on 2 or more consecutive tests
- Elevated serum TBL to ≥2 × ULN (if baseline TBL <1.5 × ULN) (except for cases of known Gilbert's syndrome)
    - In participants with baseline TBL ≥1.5 × ULN, the threshold should be TBL ≥2 × baseline
- Elevation of serum ALP to ≥2 × ULN on 2 or more consecutive blood tests (if baseline ALP <1.5 × ULN)
    - In participants with baseline ALP ≥1.5 × ULN, the threshold is ALP ≥2 × baseline on 2 or more consecutive blood tests
- Hepatic event considered to be an SAE
- Discontinuation of study intervention due to a hepatic event.

Note: The interval between the 2 consecutive blood tests should be at least 2 days.

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

The definitions of the following events can be found in Appendix 3 (Section 10.3):

- AEs
- SAEs
- Product complaints (PCs)

These events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or 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 or study (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.

Investigators are responsible for monitoring the safety of participants who have entered this study and for alerting Lilly or its designee to any event that seems unusual, even if this event may be considered an unanticipated benefit to the participant.

The investigator is responsible for the appropriate medical care of participants during the study.

After the initial report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs 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 PCs, the investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/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 informed consent form (ICF)	Participation in study has ended	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 with study procedures	Signing of the ICF	Start of intervention	Within 24 hours of awareness	SAE paper form	SAE paper form
SAE# and SAE updates – after start of study intervention	Start of intervention	Participation in study has ended	Within 24 hours of awareness	SAE paper form	SAE paper form
SAE* – 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

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-up Method of Reporting
Pregnancy					
Pregnancy in female partners of male participants	After the start of study intervention	1 week after the last dose	Within 24 hours (see Section 8.3.2)	Pregnancy paper form	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 hours of awareness	PC form	N/A
PC not associated with an SAE	Start of study intervention	End of study intervention	Within 1 business day of awareness	PC form	N/A
Updated PC information	—	—	As soon as possible upon site awareness	Originally PC 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	PC form	

* SAEs should not be reported unless the investigator deems them to be possibly related to study treatment or study participation.

8.3.2. Pregnancy

Collection of pregnancy information

Male participants with partners who become pregnant

- The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive study intervention.
- After learning of a pregnancy in the female partner of a study participant, the investigator will obtain a consent to release information from the pregnant female 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 female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor.

Generally, the follow-up will be no longer than 6 to 8 weeks following 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.

8.4. Pharmacokinetics

Venous blood samples of approximately 2 mL will be collected for measurement of plasma concentrations of rosuvastatin and pirtobrutinib as specified in the SoA (Section 1.3).

A maximum of 3 samples may be collected at additional time points during the study if warranted and agreed upon between the investigator and the sponsor.

Instructions for the collection and handling of biological samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

8.4.1. Bioanalysis

Samples will be analyzed at a laboratory approved by the sponsor and stored at a facility designated by the sponsor.

Concentrations of rosuvastatin and pirtobrutinib will be assayed using a validated liquid chromatography tandem mass spectrometry (LC-MS/MS) method.

Bioanalytical samples collected to measure investigational product concentrations will be retained for a maximum of 1 year following last participant visit for the study. During this time, samples remaining after the bioanalyses may be used for exploratory analyses such as metabolism and/or protein binding work.

8.5. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.6. Genetics

A blood sample will be collected at screening to determine genetic polymorphisms for participants to meet eligibility criteria prior to enrollment (Section 5.2 and Section 5.2.1).

A separate blood sample will be collected for storage for potential pharmacogenetic analysis as specified in the SoA (Section 1.3). See Appendix 5 (Section 10.5) for information regarding genetic research.

8.7. Biomarkers

Biomarkers are not evaluated in this study.

8.8. Immunogenicity Assessments

Immunogenicity is not evaluated in this study.

8.9. Health Economics

This section is not applicable for this study.

9. Statistical Considerations

The statistical analysis plan (SAP) 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.

9.1. Statistical Hypotheses

The primary objective variables will be evaluated to assess the potential DDI. No significant DDI for rosuvastatin will be concluded if the respective 90% confidence interval for area under the concentration versus time curve from time zero to infinity (AUC[0-∞]) and maximum observed drug concentration (C_{max}) is completely contained within the no-effect boundaries (0.80, 1.25).

9.2. Analyses Sets

The following populations are defined:

Population	Description
Entered	All participants who sign the ICF.
Enrolled	All participants assigned to study intervention, regardless of whether they take any doses.
Safety	All participants who receive at least 1 dose of rosuvastatin. Participants will be analyzed according to the intervention they actually received.
Pharmacokinetic	All participants who receive at least 1 dose of rosuvastatin and have evaluable PK data.

9.2.1. Study Participant Disposition

All participants who discontinue from the study will be identified and the extent of their participation in the study will be reported. If known, a reason for their discontinuation will be given.

A detailed description of participant disposition will be provided at the end of the study.

9.2.2. Study Participant Characteristics

The participant's age, sex, weight, height, and other demographic characteristics will be recorded.

9.3. Statistical Analyses

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

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

in the SAP and the clinical study report. Additional exploratory analyses of the data will be conducted as deemed appropriate.

Study results may be pooled with the results of other studies for safety and population PK analysis purposes to avoid issues with post-hoc analyses and incomplete disclosures of analyses.

9.3.1. Pharmacokinetic Analyses

All PK analyses will be made using the Pharmacokinetic Population.

9.3.1.1. Pharmacokinetic Parameter Estimation

PK parameter estimates for rosuvastatin will be calculated by standard noncompartmental methods of analysis.

The primary parameters for analysis will be C_{max} and AUC(0-∞) of rosuvastatin. Other noncompartmental parameters, such as t_{max}, $t_{1/2}$, apparent clearance, and apparent volume of distribution may be reported.

Blood samples collected for the PK of pirtobrutinib alone will be used to determine plasma concentration only, to ensure sufficient exposure.

9.3.1.2. Pharmacokinetic Statistical Inference

PK parameters will be evaluated to estimate drug interaction for rosuvastatin with single (Day 6) and multiple (Day 13) doses of pirtobrutinib. A subject may be excluded from the PK summary statistics and statistical analysis if the subject has an AE of vomiting that occurs at or before 2 times median t_{max}.

Log-transformed C_{max} and AUC(0-∞) parameters for rosuvastatin will be evaluated in a linear mixed-effects model with a fixed effect for treatment, and a random effect for participant. The treatment differences will be back transformed to present the ratios of geometric means and the corresponding 90% confidence interval.

The t_{max} will be analyzed using a Wilcoxon signed rank test. Estimates of the median difference based on the observed medians, 90% confidence intervals, and p-values from the Wilcoxon test will be calculated.

9.3.2. Safety Analyses

All safety analyses will be made using the Safety Population.

9.3.2.1. Clinical Evaluation of Safety

All investigational product and protocol procedure AEs will be listed, and if the frequency of events allows, safety data will be summarized using descriptive methodology.

The incidence of AEs for each treatment will be presented by severity and by association with investigational product as perceived by the investigator. AEs reported to occur prior to enrollment will be distinguished from those reported as new or increased in severity during the study. Each AE will be classified by the most suitable term from the medical regulatory dictionary. AEs by day of onset will be presented.

The number of SAEs will be reported.

9.3.2.2. Statistical Evaluation of Safety

Safety parameters that will be assessed include safety laboratory parameters and vital signs. The parameters will be listed, and summarized using standard descriptive statistics. Additional analysis will be performed if warranted upon review of the data.

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.

9.5. Sample Size Determination

10. Supporting Documentation and Operational Considerations

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

10.1.1. Regulatory and Ethical Considerations

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

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
- Applicable ICH Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations.

The protocol, protocol amendments, ICF, Investigator's Brochure (IB), and other relevant documents (for example, advertisements) must be submitted to an institutional review board (IRB)/independent ethics committee (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 the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of study conduct for participants under their responsibility and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

Investigator sites are compensated for participation in the study as detailed in the clinical trial agreement.

10.1.2. Informed Consent Process

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

Participants must be informed that their participation is voluntary. Participants 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.

Participants must be reconsented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the participant and is kept on file.

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

10.1.3. Data Protection

Participants will be assigned a unique identifier by the sponsor. Any participant 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.

The participant must be informed 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 data protection, information security and data integrity. These processes include appropriate contingency plan(s) for appropriate and timely response in the event of a data security breach.

10.1.4. Dissemination of Clinical Study Data

Communication of Suspended or Terminated Dosing

If a decision is taken to suspend or terminate dosing in the study due to safety findings, this decision will be communicated by Lilly to all investigators (for example, by phone and/or email) as soon as possible. It will be a requirement that investigators respond upon receipt to confirm that they understand the communication and have taken the appropriate action prior to further dosing any participants with study intervention. Any investigator not responding will be followed up by Lilly personnel prior to any further planned dosing. If a dose is planned imminently, Lilly personnel will immediately, and continually, use all efforts to reach investigators until contact is made and instructions verified.

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.

Data

The sponsor does not proactively share data from Phase 1 clinical studies. Requests for access to Phase 1 clinical study data are evaluated on a case-by-case basis taking into consideration the ability to anonymize the data and the nature of the data collected.

10.1.5. 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. Source data may include laboratory tests, medical records, and clinical notes.

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

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 (e.g., contract research organizations).

Study monitors will perform ongoing source data verification to confirm that data entered 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 (CTA) unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

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, and/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 electronic data capture system 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 electronic data capture 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.

10.1.6. 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 Section 10.1.5.

10.1.7. Study and Site Start and Closure

First Act of Recruitment

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

Study or Site Termination

The sponsor 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:

- Discontinuation of further study intervention development.

For site termination:

- 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
- 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.

10.1.8. 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 if the results are deemed to be of significant medical importance.

10.2. Appendix 2: Clinical Laboratory Tests

The tests detailed in the table below will be performed by the local laboratory.

Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.

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

Hematology	Clinical Chemistry
Hematocrit	Alanine aminotransferase
Hemoglobin	Albumin
Erythrocyte count (RBC)	Alkaline phosphatase
Mean cell volume	Aspartate aminotransferase
Mean cell hemoglobin	Bicarbonate
Mean cell hemoglobin concentration	Blood urea nitrogen
Leukocytes (WBC)	Calcium
Platelets	Chloride
Differential WBC (Absolute counts and %) of:	Cholesterol
Basophils	Creatinine
Eosinophils	Creatinine phosphokinase
Lymphocytes	Gamma-glutamyl transferase
Monocytes	Glucose (random)
Neutrophils	Potassium
	Sodium
	Total bilirubin[a]
Urinalysis	Total protein
Bilirubin	Uric acid
Blood	
Glucose	Serology[b]
Ketones	Hepatitis B surface antigen
Nitrite	Hepatitis C antibody
pH	Human immunodeficiency virus
Protein	
Specific gravity	Ethanol testing[d]
Urobilinogen	Urine drug screen (including cotinine)[e]
Microscopic examination of sediment[c]	Follicle-stimulating hormone[b,f]
	Pregnancy test[g]

Abbreviations: RBC = red blood cells; WBC = white blood cells.

Note: Results of these assays will be validated by the local laboratory at the time of testing. Additional tests may be performed or auto-calculated by the laboratory as part of its standard panel that cannot be removed. Some of the above parameters are calculated from measured values. Omission of calculated values will not be considered as a protocol violation.

[a] Direct and indirect bilirubin will be analyzed if total bilirubin is elevated.

[b] Performed at screening only.

[c] Test only if dipstick result is abnormal.

[d] Performed at check-in (Day -1) only.

[e] Performed at screening and check-in (Day -1) only.

[f] Females only to confirm postmenopausal status.

[g] Performed in serum at screening and in urine at all other times. A positive urine pregnancy test will be confirmed with a serum pregnancy test.

10.2.1. Blood Sampling Summary

This table summarizes the approximate number of venipunctures and blood volumes for all blood sampling during the study.

Protocol J2N-MC-JZNW Sampling Summary

Purpose	Blood Volume per Sample (mL)	Number of Blood Samples	Total Volume (mL)
Screening tests[a]	21.5	1	21.5
Clinical laboratory tests[a]	12.5	8	100
Rosuvastatin pharmacokinetics[b]	2	53	106
Pirtobrutinib pharmacokinetics[b]	2	15	30
Pharmacogenetics for storage	10	1	10
Total			267.5
Total for clinical purposes			270

[a] Additional samples may be drawn if needed for safety purposes.

[b] Includes additional 3 samples, if required.

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 Adverse Event

AE Definition
• 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 unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (for example, ECG, radiological scans, 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 pre-existing 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 DDI. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events <u>NOT</u> 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/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (for example, endoscopy, appendectomy): the condition that leads to the procedure is the AE.

- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of Serious Adverse Event

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

a. Results in death

b. 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.

c. 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 pre-existing condition that did not worsen from baseline is not considered an AE.

d. 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.

e. Is a congenital anomaly/birth defect

- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

f. 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

PCs

- A PC 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 PCs:
  - Deficiencies in labeling information, and
  - Use errors for device or drug-device combination products due to ergonomic design elements of the product.
- PCs related to study interventions used in clinical studies are collected in order to ensure the safety of participants, monitor quality, and to facilitate process and product improvements.
- Investigators will instruct participants to contact the site as soon as possible if he or she has a PC or problem with the study intervention so that the situation can be assessed.
- An event may meet the definition of both a PC and an AE/SAE. In such cases, it should be reported as both a PC and as an AE/SAE.

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

AE, SAE, and PC Recording

- When an AE/SAE/PC 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/PC 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 PC information is reported on the PC Form.

  Note: An event may meet the definition of both a PC and an AE/SAE. In such cases, it should be reported as both a PC 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 PC 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 make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories:

- Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- Moderate: A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
- Severe: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

  An event is defined as 'serious' when it meets at least one of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

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/or Product Information, for marketed products in their assessment.

- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- 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 a 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/SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor or designee with a copy of any post-mortem findings including histopathology.

10.3.5. Reporting of Serious Adverse Events

SAE Reporting via SAE Report

- Facsimile transmission of the SAE Report is the preferred method to transmit this information to the sponsor or designee.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE Report within the designated reporting time frames.
- Contacts for SAE reporting can be found in the SAE Report.

10.3.6. Regulatory Reporting Requirements

SAE Regulatory Reporting

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards 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 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 a SAE or other specific safety information (e.g., 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

Females of Childbearing Potential

Females are considered a woman of childbearing potential if

- they have had at least 1 cycle of menses, or
- they have Tanner 4 breast development.

Any amount of spotting should be considered menarche.

Females NOT of Childbearing Potential

Females are considered women not of childbearing potential if

- they have a congenital anomaly such as Mullerian agenesis
- they are infertile due to surgical sterilization
    - hysterectomy
    - bilateral oophorectomy
    - tubal ligation
- they are post-menopausal.

Post-Menopausal

The post-menopausal state should be defined as:

1. A female at any age at least 6 weeks post-surgical bilateral oophorectomy with or without hysterectomy, confirmed by operative note; or
2. A female at least 40 years of age and up to 55 years old with an intact uterus, not on hormone therapy*, 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

3. A female 55 or older not on hormone therapy, who has had at least 12 months of spontaneous amenorrhea, or
4. A female at least 55 years of age with a diagnosis of menopause prior to starting hormone replacement therapy

* Female participants should not be taking medications during amenorrhea such as oral contraceptives, hormones, gonadotropin-releasing hormone, anti-estrogens, selective estrogen receptor modulators (SERMs), or chemotherapy that could induce transient amenorrhea.

10.4.2. Contraception Guidance

10.4.2.1. Female Participants

Females of childbearing potential are excluded from this study.

Female participants not of childbearing potential, as defined in Section 10.4.1, may participate in this study and are not required to adhere to contraceptive requirements.

All female participants must test negative for pregnancy prior to initiation of treatment as indicated by a negative serum pregnancy test at the screening visit followed by a negative urine pregnancy test within 24 hours prior to exposure (Day -1). A positive urine test will be confirmed with a serum pregnancy test.

10.4.2.2. Male Participants

Male participants, regardless of their fertility status, with partners who are non-pregnant females of childbearing potential, must agree to either

1. remain abstinent (if this is their preferred and usual lifestyle), or
2. use condoms with spermicide plus 1 additional highly effective contraception method (see Section 10.4.3), during intercourse.

They must agree to adhere to these restrictions for the duration of the study and for 6 months after the last dose of study intervention.

Male participants with pregnant partners must agree to use condoms with spermicide during intercourse.

All male participants should refrain from sperm donation for the duration of the study and for 6 months after the last dose of study intervention.

10.4.3. Contraception Methods

This table illustrates examples of highly effective, effective, and ineffective forms of contraception.

Methods	Examples
Highly effective contraception	• combination oral contraceptive pill and mini-pill • implanted contraceptives • injectable contraceptives • contraceptive patch (only women <198 pounds or 90 kg) • total abstinence • vasectomy (if only sexual partner) • fallopian tube implants (if confirmed by hysterosalpingogram) • combined contraceptive vaginal ring, or • intrauterine devices

Effective contraception	• male or female condoms with spermicide
	• diaphragms with spermicide or cervical sponges
	• barrier method with use of a spermicide
	  ○ condom with spermicide
	  ○ diaphragm with spermicide, or
	  ○ female condom with spermicide

	Note: The barrier method must include use of a spermicide (i.e., condom with spermicide, diaphragm with spermicide, female condom with spermicide) to be considered effective. Male and female condoms should not be used in combination.
Ineffective forms of contraception	• spermicide alone • immunocontraceptives • periodic abstinence • fertility awareness (calendar method, temperature method, combination of above 2, cervical mucus, symptothermal) • withdrawal • post coital douche • lactational amenorrhea

10.5. Appendix 5: Genetics

10.6. Appendix 6: Liver Safety: Suggested Actions and Follow-up Assessments

See Section 8.2.7.1 for guidance on appropriate test selection.

The Lilly-designated central laboratory must complete the analysis of all selected testing except for microbiology testing.

Local testing may be performed in addition to central testing when necessary for immediate participant management.

Results will be reported if a validated test or calculation is available.

Hematology	**Clinical Chemistry**
Hemoglobin	Total bilirubin (TBL)
Hematocrit	Direct bilirubin
Erythrocytes (RBCs - red blood cells)	Alkaline phosphatase (ALP)
Leukocytes (WBCs - white blood cells)	Alanine aminotransferase (ALT)
Differential:	Aspartate aminotransferase (AST)
Neutrophils, segmented	Gamma-glutamyl transferase (GGT)
Lymphocytes	Creatine kinase (CK)
Monocytes	**Other Chemistry**
Basophils	Acetaminophen
Eosinophils	Acetaminophen protein adducts
Platelets	Alkaline phosphatase isoenzymes
Cell morphology (RBC and WBC)	Ceruloplasmin
	Copper
Coagulation	Ethyl alcohol (EtOH)
Prothrombin time, international normalized ratio (INR) (PT-INR)	Haptoglobin
Serology	Immunoglobulin IgA (quantitative)
Hepatitis A virus (HAV) testing:	Immunoglobulin IgG (quantitative)
HAV total antibody	Immunoglobulin IgM (quantitative)
HAV IgM antibody	Phosphatidylethanol (PEth)
Hepatis B virus (HBV) testing:	**Urine Chemistry**
Hepatitis B surface antigen (HBsAg)	Drug screen
Hepatitis B surface antibody (anti-HBs)	Ethyl glucuronide (EtG)
Hepatitis B core total antibody (anti-HBc)	**Other Serology**
Hepatitis B core IgM antibody	Anti-nuclear antibody (ANA)
Hepatitis B core IgG antibody	Anti-smooth muscle antibody (ASMA) [a]
HBV DNA [d]	Anti-actin antibody [b]

Hepatitis C virus (HCV) testing:	Epstein-Barr virus (EBV) testing:
HCV antibody	EBV antibody
HCV RNA [d]	EBV DNA [d]
Hepatitis D virus (HDV) testing:	Cytomegalovirus (CMV) testing:
HDV antibody	CMV antibody
Hepatitis E virus (HEV) testing:	CMV DNA [d]
HEV IgG antibody	Herpes simplex virus (HSV) testing:
HEV IgM antibody	HSV (Type 1 and 2) antibody
HEV RNA [d]	HSV (Type 1 and 2) DNA [d]
Microbiology [c]	Liver kidney microsomal type 1 (LKM-1) antibody
Culture:	
Blood	
Urine	

a Not required if anti-actin antibody is tested.

b Not required if anti-smooth muscle antibody (ASMA) is tested.

c Assayed ONLY by investigator-designated local laboratory; no central testing available.

d Reflex/confirmation dependent on regulatory requirements, testing availability, or both.

10.7. Appendix 7: Abbreviations

Term	Definition
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC(0-∞)	area under the concentration versus time curve from time zero to infinity
BCRP	breast cancer resistance protein
BTK	Bruton's tyrosine kinase
CFR	Code of Federal Regulations
C_{max}	maximum observed drug concentration
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.
CP	clinical pharmacologist
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 study participant.
CRP	clinical research physician: Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician or other medical officer.
CRU	clinical research unit
CV	coefficient of variation
DDI	drug-drug interaction
ECG	electrocardiogram
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 ICF directly or through their legally acceptable representatives.

GCP	good clinical practice
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee
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 ICF.
investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical study, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
IRB	institutional review board
participant	Equivalent to CDISC term "subject": an individual who participates in a clinical study, either as recipient of an investigational medicinal product or as a control
PC	product complaint
PK	pharmacokinetic(s)
QD	once daily
QTc	corrected QT interval
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.
SoA	Schedule of Activities
$t_{1/2}$	terminal half-life
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.
t_{max}	time to maximum drug concentration
ULN	upper limit of normal

11. References

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Leo Document ID = 12ff9aea-8f09-411a-9bf2-2305c169a69d

Approver: PPD

Approval Date & Time: 22-Dec-2021 14:39:57 GMT

Signature meaning: Approved

Approver: PPD

Approval Date & Time: 22-Dec-2021 15:40:28 GMT

Signature meaning: Approved