Protocol Addendum J2G-MC-JZPB (a)

A Phase 1, Open-Label, Drug Interaction Study to Investigate the Effect of Single Dose Selpercatinib on the Pharmacokinetics of Rosuvastatin in Healthy Participants

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Approval Date: 19-May-2023

Title Page

Protocol Title:

A Phase 1, Open-Label, Drug Interaction Study to Investigate the Effect of Single Dose Selpercatinib on the Pharmacokinetics of Rosuvastatin in Healthy Participants

Protocol Number: J2G-MC-JZPB

Amendment Number: a

Compound: LY3527723 (selpercatinib)

Brief Title:

A drug interaction study to investigate the effect of selpercatinib on the pharmacokinetics of rosuvastatin.

Study Phase: Phase 1

Acronym: JZPB

Sponsor Name: Eli Lilly and Company

Legal Registered Address: Eli Lilly and Company, Indianapolis, Indiana USA 46285

Regulatory Agency Identifier Number:

IND: 133193

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

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Medical Monitor Name and Contact Information will be provided separately.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Original Protocol	*03-Apr-2023*

Amendment [a]

Overall Rationale for the Amendment:

The protocol is being amended to remove language specific to case report form entry.

Section # and Name	Description of Change	Brief Rationale
Section 8 Study Assessments and Procedures	Removed bullet 5.	To remove language regarding sample collection actual time case report form (CRF) entry for consistency with the study electronic case report form (eCRF) build.

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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 Dose Selpercatinib on the Pharmacokinetics of Rosuvastatin in Healthy Participants

Brief Title:

A drug interaction study to investigate the effect of selpercatinib on the pharmacokinetics of rosuvastatin.

Regulatory Agency Identifier Number:

IND: 133193

Rationale:

Rosuvastatin is a commonly used index substrate for breast cancer resistance protein (BCRP) (FDA, 2021). Selpercatinib may potentially inhibit BCRP in the intestine according to in vitro evaluation. 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 selpercatinib.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To evaluate the effect of a single dose of selpercatinib on BCRP activity in healthy participants	• C_{max} and $AUC_{(0-\infty)}$ of rosuvastatin
Secondary	
• To describe the safety and tolerability of rosuvastatin in combination with selpercatinib in healthy participants	• Incidence of TEAEs and SAEs

Abbreviations: $AUC_{(0-\infty)}$ = 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:

Study J2G-MC-JZPB is a Phase 1, open-label, fixed-sequence, drug interaction study to investigate the effect of a single dose of selpercatinib on the PK of rosuvastatin in healthy participants.

Brief Summary:

The purpose of this study is to investigate a potential DDI by measuring PK of rosuvastatin with selpercatinib in healthy participants.

Study details include:

- The study duration will be approximately 8 weeks.
- The study intervention will be administered on Days 1 and 5.
- The visit frequency will be 9 continuous days in the clinical research unit (CRU).

Study Population:

Healthy participants will be enrolled in this study.

Number of Participants:

Approximately 28 participants will be enrolled to ensure that a least 20 evaluable participants complete the study.

Intervention Groups and Duration:

All participants will be screened for inclusion within 42 days prior to enrollment. Eligible participants will be admitted to the CRU on Day -1 and remain resident in the CRU until discharge on Day 8. A follow-up visit will be performed 7 to 10 days (Days 12 to 15) after the final dose of study intervention.

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

- Day 1: 20 mg rosuvastatin alone
- Day 5: 20 mg rosuvastatin coadministered simultaneously with 160 mg selpercatinib

Ethical Considerations of Benefit/Risk:

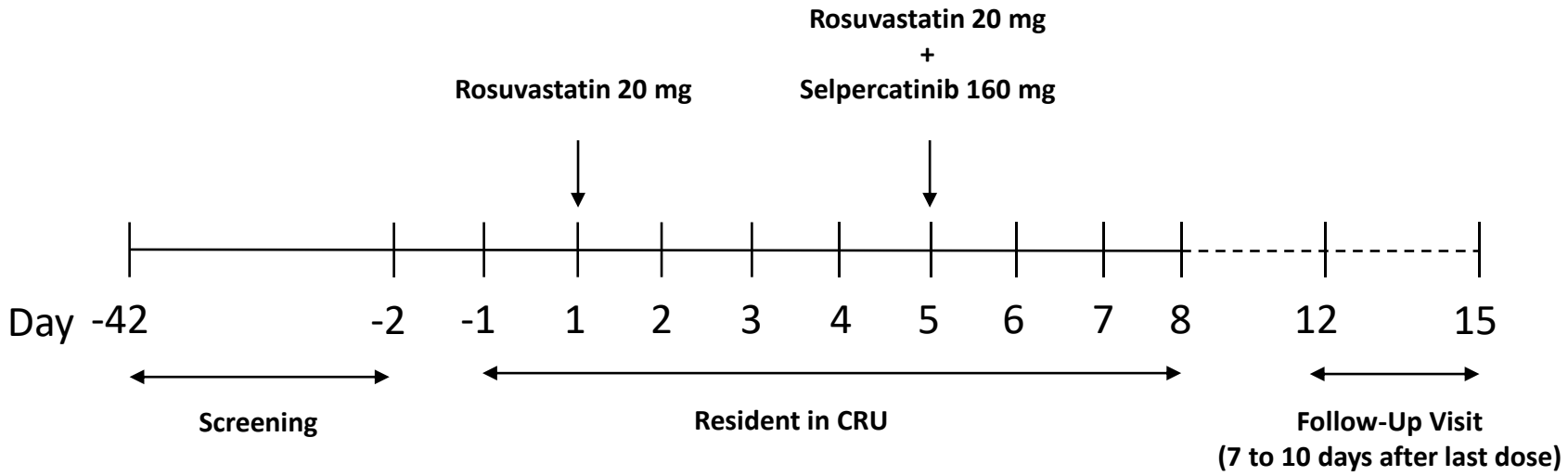
The following are the risks and discomforts associated with selpercatinib: dry mouth, diarrhea, hypertension, fatigue, constipation, alanine aminotransferase (ALT)/aspartate aminotransferase (AST) elevation, headache, nausea, edema peripheral, abdominal pain, rash, electrocardiogram QT prolonged, cough, vomiting, dyspnea, and increased blood creatinine.

Adverse events of special interest include hypersensitivity, liver injury, QT prolongation, and hypertension. Therefore, these reactions will be monitored during the course of the study.

The following are the risks and discomforts associated with rosuvastatin: headache, myalgia, abdominal pain, asthenia, nausea, ALT/AST elevation, myopathy, and rhabdomyolysis.

Data Monitoring Committee: No

1.2. Schema



Abbreviation: CRU = clinical research unit

1.3. Schedule of Activities (SoA)

Study Procedure	Screening	Treatment									FU/ED	Comments
Study Day	-42 to -2	-1	1	2	3	4	5	6	7	8	12 to 15	
Informed consent	X											
Medical history and demographics	X	X										
Admission to CRU		X										
Discharge from CRU										X		
Outpatient visit	X										X	
Participant eligibility	X	X										
Height and weight	X	X									X	Height: screening only.
Physical examination		X								X		Day -1: Full examination. Day 8: Symptom-driven examination.
Pregnancy test	X	X									X	Serum pregnancy test: screening. Urine pregnancy test: all other time points.
FSH	X											See Section 10.4.1.
Serology	X											
Clinical laboratory tests	X	X			X		P		X		X	
12-lead ECG (hr)	X		P				P, 2, 4	24	48	72	X	
Vital signs and body temperature (supine) (hr)	X	X	P	24	X	X	P, 1, 2	24	X	X	X	Temperature: screening and Day -1.
Ethanol test	X	X										
Urine drug screen	X	X										

Study Procedure	**Screening**	**Treatment**									**FU/ED**	**Comments**
Study Day	-42 to -2	-1	1	2	3	4	5	6	7	8	12 to 15	
Genetic blood sample for screening	X											
Pharmacogenetic blood sample for storage			P									
Rosuvastatin administration			X				X					
Selpercatinib administration							X					
Rosuvastatin PK samples (hr)	CCI											
Selpercatinib PK samples (hr)												
Plasma coproporphyrin I samples (hr)												
Adverse events			X	X	X	X	X	X	X	X	X	
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	

Abbreviations: CRU = clinical research unit; ECG = electrocardiogram; ED = early discontinuation; FSH = follicle stimulating hormone; FU = follow-up; hr = hour; P = predose; PK = pharmacokinetics.

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). Selpercatinib may potentially inhibit BCRP in the intestine according to in vitro evaluation. 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 selpercatinib.

2.2. Background

Selpercatinib (LY3527723, Retevmo®) is a an orally available, highly selective, adenosine triphosphate (ATP)-competitive small molecule inhibitor of the *REarranged during Transfection (RET)* gene receptor tyrosine kinase (RTK) approved by the FDA for the treatment of

- adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with a *RET* gene fusion, as detected by an FDA-approved test
- adult and pediatric patients 12 years of age and older with advanced or metastatic medullary thyroid cancer (MTC) with a *RET* mutation, as detected by an FDA-approved test, who require systemic therapy
- adult and pediatric patients 12 years of age and older with advanced or metastatic thyroid cancer with a *RET* gene fusion, as detected by an FDA-approved test, who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate)
- adult patients with locally advanced or metastatic solid tumors with a *RET* gene fusion that have progressed on or following prior systemic treatment or who have no satisfactory alternative treatment options

Across clinical studies, single oral doses of selpercatinib were administered over a range of 20 to 720 mg. In studies (LOXO-RET-18017 and LOXO-RET-18026), multiple oral doses of 160 mg/day selpercatinib were administered orally twice daily for 10 days in healthy participants.

In healthy participants, the median (range) time to maximum drug concentration (t_{max}) of selpercatinib is 2 (1.5 to 6.0) hours and selpercatinib is eliminated with a mean (range) terminal elimination half-life ($t_{1/2}$) of 13.6 (9.82 to 19.6) hours.

More detailed information about the PK and absorption, distribution, metabolism, and excretion properties of selpercatinib may be found in the Investigator's Brochure (IB).

2.3. Benefit/Risk Assessment

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.

The single dose of selpercatinib to be given in this study is 160 mg (2 × 80-mg capsules), as it is the highest approved dose by the FDA. The safety profile of selpercatinib shows that selpercatinib is very well tolerated in healthy participants and is clinically manageable, with low rates of study drug discontinuation due to adverse events (AEs). As outlined in the IB, the most common toxicities associated with selpercatinib are monitorable and reversible, and include dry mouth, diarrhea, hypertension, fatigue, constipation, aspartate aminotransferase (AST)/ alanine aminotransferase (ALT) elevation, headache, nausea, edema peripheral, abdominal pain, rash, electrocardiogram (ECG) QT prolonged, cough, vomiting, dyspnea, and increased blood creatinine. Adverse events of special interest include hypersensitivity, liver injury, QT prolongation, and hypertension. In a recently completed DDI study with dabigatran in healthy participants (Study J2G-MC-JZJV), only 1 treatment-emergent adverse event (TEAE) considered to be related to selpercatinib was reported (dyspepsia). In a single 160-mg dose, crossover bioequivalent study in 224 healthy participants (Study J2G-MC-JZJZ), the most frequently reported TEAEs following dosing was headache (20 events in 16 participants) followed by COVID-19 (13 events in 13 participants). Four AEs of ALT increased and 2 AEs of AST increased were reported, all were mild in severity and resolved by the end of the study.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of selpercatinib may be found in the IB.

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 (ALT and 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 and reasonably expected AEs 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 a single dose of selpercatinib on BCRP activity in healthy participants	• C_{max} and $AUC_{(0-\infty)}$ of rosuvastatin
Secondary	
• To describe the safety and tolerability of rosuvastatin in combination with selpercatinib in healthy participants	• Incidence of TEAEs and SAEs
Exploratory	
• To assess the exploratory measurement of plasma coproporphyrin I as biomarker of transporter OATP1B1 and OATP1B3 inhibition in healthy participants to further inform degree of transporter inhibition risk	• Plasma concentrations of biomarker coproporphyrin I: C_{max} and $AUC_{(0-24)}$

Abbreviations: $AUC_{(0-\infty)}$ = area under the concentration versus time curve from time zero to infinity; $AUC_{(0-24)}$ =area under the concentration versus time curve from time zero to 24 hours; BCRP = breast cancer resistance protein; C_{max} = maximum observed drug concentration; OATP = organic anion transporting polypeptide; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

4. Study Design

4.1. Overall Design

Study J2G-MC-JZPB is a Phase 1, open-label, fixed-sequence, drug interaction study to investigate the effect of a single dose of selpercatinib on the PK of rosuvastatin in healthy participants.

The schema in Section 1.2 illustrates the study design.

Approximately 28 participants will be enrolled to ensure that at least 20 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 8.

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

- Day 1: 20 mg rosuvastatin alone
- Day 5: 20 mg rosuvastatin coadministered simultaneously with 160 mg selpercatinib

Pharmacokinetic 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 8 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 to 10 days (Days 12 to 15) after the final dose of rosuvastatin coadministered with a single dose of selpercatinib. 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

To allow each participant 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 from label (19 hours; Crestor Prescribing Information, 2020) or observed from Study J2N-MC-JZNW (geometric mean of 8.21 hours with range of 3.02 to 39.8 hours), a period of 4 days between rosuvastatin doses is considered sufficient time for the study intervention to washout.

The PK of rosuvastatin will be evaluated after a single dose on Day 1 and again on Day 5, coadministered simultaneously with selpercatinib, to assess the effect of selpercatinib on intestinal BCRP.

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

4.3. Justification for Dose

The single dose of 160 mg is the highest approved dose for selpercatinib.

The dose of rosuvastatin (20 mg) has been chosen as this is the clinically relevant dose considered safe to administer and has been used concomitantly in previous clinical DDI studies.

4.4. End of Study Definition

The end of the study is defined as 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 the 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 the human BCRP transporter (also known as ABCG2) and the human organic anion transporting polypeptide 1B1 (OATP1B1) transporter (also known as SLCO1B1) genotyping, screening medical history, physical examination, vital signs, clinical laboratory tests, and ECG. The nature of any conditions present at the time of the physical examination and any preexisting conditions will be documented.

The inclusion and exclusion criteria used to determine eligibility should be applied at screening only unless otherwise specified, and not continuously throughout the trial. Clinical laboratory tests and vital signs may be repeated from screening through Day -1 at the discretion of the investigator in order to confirm eligibility.

Screening may occur up to 42 days prior to enrollment (Day 1). 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 screening tests and procedures: body weight, vital signs, clinical laboratory tests, ECG, and pregnancy test (females only).

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

5.1. Inclusion Criteria

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

Age

1. Participant must be 18 to 65 years of age inclusive, at the time of signing the informed consent.

Race

2. Participant must be Caucasian.

Type of Participant and Disease Characteristics

3. Participants who are overtly healthy as determined by medical evaluation including medical history, physical examination, vital signs, and ECGs.
4. Participants who have clinical laboratory test results within the 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.
5. Participants who have venous access sufficient to allow for blood sampling as per the protocol.

Weight

6. Body mass index within the range 19.0 to 32.0 kg/m^2 (inclusive).

Sex and Contraceptive/Barrier Requirements

7. Male and/or female

   Contraceptive use by participants should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. For the contraception requirements of this protocol, see Appendix 4, Section 10.4.

Informed Consent

8. 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.

Other Inclusion Criteria

9. Are reliable and willing to make themselves available for the duration of the study and are willing to follow study procedures.

5.2. Exclusion Criteria

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

Medical Conditions

10. Have known allergies to selpercatinib-related compounds or any components of the formulation of selpercatinib, or history of significant atopy.
11. Have a known allergy, intolerance, or hypersensitivity to any component of rosuvastatin that would pose an unacceptable risk to the participant.
12. Have a significant history of allergic reactions to medications or food products.
13. Have a clinically significant abnormal blood pressure and/or pulse rate as determined by the investigator.
14. Have a 12-lead ECG abnormality that, in the opinion of the investigator,

    - increases the risks associated with participating in the study
    - a QT interval corrected using Fridericia's formula (QTcF)
      - >450 msec for males or
      - >470 msec for females

    If an ECG parameter is out of range in the screening ECG, the site may perform 2 repeat ECGs and average the 3 results to assess eligibility.

15. Have clinically significant active cardiovascular disease or history of myocardial infarction within 6 months prior to the planned start of dosing.
16. Have a significant previous or current history or presence of cardiovascular, respiratory, renal, gastrointestinal, endocrine, hematological, or neurological disorders 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. NOTE: history of uncomplicated appendectomy is considered acceptable.
17. Show a history of central nervous system conditions such as strokes, transient ischemic attacks, significant head trauma, seizures, central nervous system infections, migraine, brain surgery, or any other neurological conditions that, in the opinion of the investigator, increase the risk of participating in the study.
18. Have a history or presence of neuropsychiatric disease (e.g., bipolar disorder, schizophrenia, depression) considered as clinically significant by the investigator.
19. 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.
20. Have any medical conditions, medical history, or are taking any medications which are contraindicated in the selpercatinib or rosuvastatin label.
21. Are lactating.

Prior/Concomitant Therapy

22. Vaccination with live vaccines within 28 days prior to screening or plans to receive such vaccines during the study. NOTE: use of non-live (inactivated) vaccinations will be allowed.
23. Have used or are intending to use over-the-counter or prescription medication, including dietary supplements and herbal medications, within 14 days prior to dosing and until study discharge (apart from occasional acetaminophen (≤3 g/24 hours), hormonal contraception, or hormone replacement therapy).

Prior/Concurrent Clinical Study Experience

24. 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.
25. Have participated, within the last 30 days of admission, 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.
26. Have previously completed or withdrawn from this study or any other study investigating selpercatinib.

Diagnostic Assessments

27. Show evidence of human immunodeficiency virus infection and/or positive human immunodeficiency virus antibodies.
28. Have a positive HCV Ab test.
    - Participants who have spontaneously cleared HCV infection (positive HCV Ab in conjunction with a negative HCV RNA test at screening, in addition to no history of HCV antibody (anti-HCV) treatment) may be included in the study.
29. Have a current infection with hepatitis B virus (HBV), that is, positive for hepatitis B surface antigen, polymerase chain reaction positive for HBV DNA or both.

Other Exclusion Criteria

30. Have c.34AA, c.421AA, or c.34GA/421CA genotypes of ABCG2 as determined through genotyping.
31. Have c.521TC and c/521CC genotypes of SLCO1B1 as determined by genotyping.
32. Have a positive pregnancy test at screening or Day -1, where applicable.
33. Are pregnant or intend to become pregnant or to breastfeed during the study.
34. Regularly use known drugs of abuse or show positive findings on drug screening.
35. Currently use or show evidence of substance abuse (including alcohol abuse) or dependence within the past 6 months based on medical history at screening visit.
36. Have donated blood of more than 500 mL within the previous 2 months of study screening.
37. Have an average weekly alcohol intake that exceeds 21 units per week (males ≤65 years old) and 14 units per week (females).
38. Are unwilling to stop alcohol consumption 48 hours prior to admission to the CRU, and while resident at the CRU. At all other times, participants must agree to consume no more than 2 units per day.
39. Smoke more than 10 cigarettes or e-cigarettes, or 3 cigars or 3 pipes, per day or are unable to abide by investigative site smoking restrictions.
40. Unwilling to limit caffeine consumption to 2 servings per day during each dosing session.
41. Are investigator site personnel directly affiliated with this study and/or their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.
42. Are Lilly employees or are an employee of any third-party involved in the study who require exclusion of their employees.
43. 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

Human BCRP, which is encoded by the gene 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 selpercatinib and rosuvastatin will be evaluated in this study.

To reduce the number of participants who need to be screened for the study, participation is limited to Caucasians because c.421C>A and c.34G>A polymorphisms occur at lower frequencies in Caucasians (Kim et al, 2010).

Human OATP1B1 transporter, which is encoded by the gene SLCO1B1, is also polymorphic. To minimize variability in rosuvastatin PK, 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

- Standard meals will be provided at all times while participants are resident at the CRU, as per the CRU's policy.

5.3.2. Substance Use: Caffeine, Alcohol, and Tobacco

- During each dose administration, participants will be allowed to ingest 2 servings per day of caffeine or xanthine containing products.
- Participants will abstain from alcohol for 48 hours prior to admission until discharge from the CRU.
- Participants who use tobacco products (including, but not limited to, cigarettes, pipes, cigars, chewing tobacco, nicotine patches, nicotine lozenges, nicotine gum, or vaping products) will be instructed that use of nicotine-containing products (including nicotine patches) will not be permitted while they are in the clinical unit.

5.3.3. Activity

Participants will abstain from strenuous exercise for 48 hours before each blood collection for clinical laboratory tests. Participants may take part in light recreational activities during the study (for example, 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 not be rescreened.

5.5. Criteria for Temporarily Delaying Enrollment/Randomization/Administration of Study Intervention of a Participant

Not applicable.

6. Study Intervention(s) 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 coadministered with selpercatinib.

This table lists the interventions used in this clinical study.

Intervention Name	Selpercatinib	Rosuvastatin (Crestor)
Dose Formulation	Capsule	Tablet
Dosage Level(s)	2 × 80-mg capsules (160-mg dose)	1 × 20-mg tablet (20-mg dose)
Route of Administration	Oral	Oral
Dosing instructions	2 capsules taken on Day 5	1 tablet taken on Day 1 and Day 5

Packaging and labeling

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

6.1.1. Administration Details

Rosuvastatin will be administered orally with approximately 240 mL of room temperature water in the morning of Day 1 (see Section 1.3) in a sitting position. When rosuvastatin and selpercatinib are administered simultaneously on Day 5, approximately 240 mL of room temperature water will be used. Selpercatinib should be administered at the same time as 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.

On Day 1, rosuvastatin will be administered alone after an overnight fast of at least 8 hours and participants will remain fasting for approximately 4 hours postdose. On Day 5, rosuvastatin and selpercatinib will be coadministered simultaneously 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.

6.2. Preparation, Handling, Storage, and Accountability

- The investigator or designee must confirm appropriate storage conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
- Only participants enrolled in the study may receive study intervention. Only authorized study personnel may supply, prepare, or administer study intervention.
- All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized study personnel.
- The investigator or authorized study personnel are responsible for study intervention accountability, reconciliation, and record maintenance (that is, receipt, reconciliation, and final disposition records).
- 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.
- Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy Manual.

6.3. Assignment to Study Intervention

This is a nonrandomized, open-label study.

6.4. Blinding

Not applicable as this is an open-label study.

6.5. Study Intervention Compliance

Study intervention will be administered 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 will be provided to the sponsor as requested.

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

6.6. Dose Modification

Dose modification is not permitted in this study.

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

Not applicable.

6.8. Treatment of Overdose

For this study, any dose of selpercatinib greater than 160 mg or rosuvastatin greater than 20 mg within a 24-hour time period will be considered an overdose.

Sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should:

- Contact the medical monitor immediately.
- Closely monitor the participant for any AE/serious adverse event (SAE) and laboratory abnormalities as medically appropriate.
- Obtain a plasma sample for PK analysis if requested by the medical monitor (determined on a case-by-case basis).
- Document the quantity of the excess dose as well as the duration of the overdose in the case report form (CRF).

6.9. Prior and Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) 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 medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Participants must abstain from taking prescription or nonprescription drugs (including vitamins and dietary or herbal supplements) within 14 days prior to dosing and until discharge from the study, unless, in the opinion of the investigator and sponsor, the medication will not interfere with the study.

If concomitant use of strong and moderate CYP3A inhibitors or drugs known to prolong the QT interval cannot be avoided, monitor the QT interval with ECGs for approximately 4 hours following the dose of selpercatinib.

Acetaminophen, at doses of ≤3 g/24 hours, is permitted for use at the discretion of the investigator for the treatment of headache, etc. Other concomitant medication may be considered on a case-by-case basis by the investigator in consultation with the medical monitor if required.

Contraceptive medication is permitted as per the contraception requirements (Appendix 4 [Section 10.4]), and hormone replacement therapy is also allowed.

Other medication may be considered on a case-by-case basis by the investigator in consultation with the Lilly clinical pharmacologist (CP)/clinical research physician (CRP), or designee.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

Participants discontinuing from the study prematurely for any reason must complete AE and follow-up procedures per Section 1.3 of this protocol.

Discontinuation of the study as a whole are handled as part of Appendix 1 (Section 10.1.9).

7.1. Discontinuation of Study Intervention

When necessary, a participant may be permanently discontinued from study intervention. If so, the participant will discontinue the study intervention (treatment), thereby discontinuing the treatment period, and will remain in the study to complete procedures for an early discontinuation visit and post-treatment follow-up, if applicable, as shown in the SoA.

A participant should be permanently discontinued from the study if

- the participant becomes pregnant during the study,
- in the opinion of the investigator, the participant should permanently discontinue the study intervention for safety reasons

7.1.1. Liver Chemistry Stopping Criteria

Study drug will be discontinued for a participant if liver chemistry stopping criteria are met.

Phase 1 Liver Chemistry Stopping Algorithm

The study drug 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	For participants with Gilbert's syndrome: If baseline direct bilirubin is >0.5 mg/dL, then doubling of direct bilirubin should be used for drug interruption decisions rather than TBL>2x 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	For participants with Gilbert's syndrome: If baseline direct bilirubin is >0.5 mg/dL, then doubling of direct bilirubin should be used for drug interruption 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.

Resuming study drug after elevated liver tests

Resumption of the study drug can be considered only in consultation with the Lilly designated medical monitor and only if the liver test results return to baseline and if a self-limited non-drug etiology is identified. Otherwise, the study drug should be discontinued.

7.1.2. QTc Stopping Criteria

If a clinically significant finding is identified (including, but not limited to changes from baseline QTcF) after enrollment, the investigator or qualified designee will determine if the participant can continue on the study intervention and if any change in participant management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

7.2. Participant Discontinuation/Withdrawal from the Study

Discontinuation is expected to be uncommon.

A participant may withdraw from the study:

- at any time at the participant's own request for any reason or without providing any reason
- at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons
- if enrolled in any other clinical study involving an investigational product, or enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study
- if the participant, for any reason, requires treatment with a therapeutic agent that is prohibited by the protocol.

At the time of discontinuing from the study, if possible, the participant will complete procedures for an early discontinuation visit, as shown in the SoA. If the participant has not already discontinued the study intervention, the participant will be permanently discontinued from the study intervention.

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

7.3. Lost to Follow up

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

8.2.1. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, dermatological, and neurological systems. Height and weight will also be measured and recorded.
- A symptom-directed physical examination will be performed at other visits, as deemed necessary by the investigator.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.2. 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 the supine position. When possible, measurements of blood pressure and pulse rate should be performed at approximately the same time of day at each scheduled time point.
- If orthostatic measurements are required, participants should be supine for at least 5 minutes and stand for at least 3 minutes. Unscheduled orthostatic vital signs should be assessed, if possible, during any AE of dizziness or posture-induced symptoms.
- Additional vital signs may be measured during each study period if warranted.
- If the participant feels unable to stand, supine vital signs only will be recorded.

8.2.3. Electrocardiograms

- For each participant, a single 12-lead digital ECG will be collected according to the SoA (see Section 1.3). Electrocardiograms 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. Electrocardiograms may be obtained at additional times, when deemed clinically necessary. All ECGs recorded should be stored at the investigational site.
- Any clinically significant findings from ECGs that result in a diagnosis and that occur after the participant receives the first dose of the investigational product, should be reported to Lilly, or its designee, as an AE via eCRF.
- Electrocardiograms 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 visit(s) 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 interval 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.

8.2.4. Clinical Safety Laboratory Tests

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

- The investigator must review the laboratory results, document this review, and report any clinically relevant changes occurring during the study as an AE. The laboratory results must be retained with source documents unless a Source Document Agreement or comparable document cites an electronic location that accommodates the expected retention duration. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.
    - If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
    - All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the SoA, standard collection requirements, and laboratory manual.
- If laboratory values from non-protocol specified laboratory assessments performed at an investigator-designated local laboratory require a change in participant management or are considered clinically significant by the investigator (for example, SAE or AE), then report the information as an AE.
- If a central vendor is used for the study, Lilly or its designee will provide the investigator with the results of laboratory tests analyzed by a central vendor.

8.2.5. Pregnancy Testing

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

8.2.6. Safety Monitoring

The Lilly CP or CRP, or designee 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:

- trends in safety data,
- laboratory analytes, and
- AEs.

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

8.2.6.1. Hepatic Safety

Close hepatic monitoring

Laboratory tests, including ALT, AST, alkaline phosphatase (ALP), total bilirubin (TBL), direct bilirubin, gamma-glutamyl transferase, and creatine kinase, should be repeated 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)

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; TBL = total bilirubin; ULN = upper limit of normal.

If the abnormality persists or worsens, clinical and laboratory monitoring, and evaluation for possible causes of abnormal liver tests should be initiated by the investigator in consultation with the Lilly-designated medical monitor. At a minimum, this evaluation should include physical examination and a thorough medical history, including symptoms, recent illnesses (for example, heart failure, systemic infection, hypotension, or seizures), recent travel, history of concomitant medications (including over-the-counter), herbal and dietary supplements, 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 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 with hepatic signs/symptoms[a], 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[a], 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)

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; TBL = total bilirubin; ULN = upper limit of normal.

[a] Hepatic signs/symptoms are severe fatigue, nausea, vomiting, right upper quadrant abdominal pain, fever, rash, 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 normalization 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 medical monitor, including tests for:

- hepatitis D virus,
- cytomegalovirus,
- Epstein-Barr virus,
- acetaminophen levels,
- acetaminophen protein adducts,
- urine toxicology screen,
- Wilson's disease,

- blood alcohol levels,
- urinary ethyl glucuronide, and
- blood 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 (hepatic safety CRF) in study participants who have abnormal liver tests during the study

Additional hepatic safety data collection in hepatic safety CRFs should be performed in study participants who meet 1 or more of the following 5 conditions:

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

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

8.2.6.2. Hypersensitivity Reactions

Many drugs, including oral agents and biologic agents, carry the risk of systemic hypersensitivity reactions. If such a reaction occurs, additional data should be provided to the sponsor in the designated CRFs.

Sites should have appropriately trained medical staff and appropriate medical equipment available when study participants are receiving study intervention. It is recommended that participants who experience a systemic hypersensitivity reaction be treated per national and international guidelines.

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

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

- AEs
- SAEs
- Product complaints (PCs)

These events will be reported by the participant.

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

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

After the initial report, the investigator is required to proactively follow each participant at subsequent visits/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.

Investigators and any qualified designees 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.

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	Start of intervention	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 to 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
Pregnancy					
Pregnancy in female participants and female partners of male participants	After the start of study intervention	Discharge from the CRU	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

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-up Method of Reporting
Updated PC information	—	—	As soon as possible upon site awareness	Originally completed Product Complaint form with all changes signed and dated by the investigator	N/A
PC (if investigator becomes aware)	Participation in study has ended	N/A	Promptly	Product Complaint form	

Abbreviations: AE = adverse event; ICF = informed consent form; N/A = not applicable; PC = product complaints; SAE = serious adverse event.

* Serious adverse events 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.

Female participants who become pregnant

- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a participant's pregnancy.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of gestational age, fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion (occurring at <20 weeks gestational age) or still birth (occurring at ≥20 weeks gestational age) is always considered to be an SAE and will be reported as such.
- Any post-study pregnancy related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in protocol Section 8.3.1. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will be withdrawn from the study. If the participant is discontinued from the study, follow the standard discontinuation process and continue directly to the follow-up phase. The follow-up on the pregnancy outcome should continue independent of intervention or study discontinuation.

8.4. Pharmacokinetics

- Venous blood samples of approximately CCI each will be collected for measurement of plasma concentrations of selpercatinib, rosuvastatin, and coproporphyrin I as specified in the SoA (Section 1.3).
- A maximum of [redacted] samples may be collected at additional time points during the study if warranted and agreed upon between the investigator and the sponsor. The timing of sampling may be altered during the course of the study based on newly available data (for example, to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.
- 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 selpercatinib and rosuvastatin will be assayed using a validated liquid chromatography with tandem mass spectrometry method.
- Concentrations of coproporphyrin I will be assayed using a validated liquid chromatography with tandem mass spectrometry method.
- Bioanalytical samples collected to measure investigational product concentrations will be retained for a maximum of 1 year following the last participant visit for the study. During this time, samples remaining after the bioanalyses may be used for exploratory analyses such as metabolism work, protein binding, or bioanalytical method cross-validation

8.5. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.6. Genetics

A blood sample for DNA isolation will be collected from participants 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 and Appendix 5 (Section 10.1.11) for details about sample retention and custody.

8.7. Biomarkers

Clinical study data indicate that the endogenous coproporphyrin I can be used to detect in vivo inhibition of hepatic OATPs; therefore, coproporphyrin I will be explored in this study as potential mechanistic biomarkers of OATP function. This may aid in mechanistic understanding of selpercatinib effect on OATPs versus BCRP.

At the visits and times specified in the SoA, venous blood samples will be collected to determine the plasma concentrations of coproporphyrin I. The actual date and 24-hour clock time of each sampling will be recorded. Refer to the SoA (Section 1.3) for *c*oproporphyrin I sampling time points.

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

9.1. Statistical Hypotheses

The primary objective will be to evaluate the effect of a single dose of selpercatinib on BCRP activity in healthy participants assessed by considering the true DDI ratio of the inhibitory effect of selpercatinib on the BCRP substrate rosuvastatin ([rosuvastatin + selpercatinib] / rosuvastatin).

Approximately 28 participants will be enrolled to ensure that at least 20 evaluable participants complete the study. A total of 20 evaluable participants will provide at least 90% coverage probability to ensure the half-width of the 90% confidence interval (CI) for the AUC ratio of rosuvastatin falls within 25% of the true ratio ([rosuvastatin + selpercatinib] / rosuvastatin).

9.2. Analyses Sets

The following populations are defined:

Population	Description
Entered	All participants who sign the ICF.
Enrolled/Safety	All participants who receive at least 1 dose of rosuvastatin.
Pharmacokinetic (Evaluable)	All participants who receive at least 1 dose of rosuvastatin and have evaluable PK data.

9.2.1. Study Participant Disposition

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.

Pharmacokinetic analyses will be conducted on data from all participants who receive at least 1 dose of rosuvastatin and have evaluable PK.

Safety analyses will be conducted for all enrolled participants who received study intervention, whether or not they completed all protocol requirements.

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. General Considerations

Handling of missing, unused, and spurious data are addressed prospectively in the overall statistical methods described in the protocol and/or in the statistical analysis plan, where appropriate. Adjustments to the planned analyses are described in the final clinical study report.

9.3.2. Primary Endpoint Analysis: Pharmacokinetic Analyses

All PK analyses will be made using the PK Population.

9.3.2.1. Pharmacokinetic Parameter Estimation

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

The primary parameters for analysis will be maximum observed drug concentration (C_{max}) and area under the concentration versus time curve from time zero to infinity ($AUC_{0-\infty}$) of rosuvastatin. Other noncompartmental parameters, such as $t_{1/2}$, t_{max}, apparent clearance, apparent volume of distribution, and area under the concentration versus time curve from time zero to time t, where t is the last time point with a measurable concentration ($AUC[0-t_{last}]$), will be reported.

Blood samples collected for the PK of selpercatinib alone will be used to determine C_{max} only to ensure sufficient selpercatinib exposure in systemic circulation.

9.3.2.2. Pharmacokinetic Statistical Inference

Pharmacokinetic parameters for rosuvastatin alone dosed on Day 1 will be compared to PK parameters for rosuvastatin with single dose of selpercatinib dosed on Day 5.

If a participant has an AE of vomiting that occurs at or before 2 times median t_{max} of either rosuvastatin or selpercatinib, the impacted period of this participant will be excluded from the PK summary statistics and statistical analysis.

Log-transformed C_{max} and $AUC_{(0-\infty)}$ of rosuvastatin will be evaluated in a linear mixed-effects model with fixed effects 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% CIs. The test treatment is rosuvastatin in the presence of selpercatinib, and reference treatment is rosuvastatin alone.

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

9.3.3. Secondary Endpoint Analysis: Safety Analyses

All safety analyses will be made using the Safety Population.

The incidence of TEAEs and SAEs will be reported separately with respect to the dose date for selpercatinib (i.e., separate events and percentages will be reported for AEs pre-selpercatinib and post-selpercatinib).

9.3.3.1. 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. Each AE will be classified by the most suitable term from the medical regulatory dictionary.

The number of SAEs will be reported.

9.3.3.2. Statistical Evaluation of Safety

Safety parameters that will be assessed include clinical 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.

Additional details can be found in the statistical analysis plan.

9.3.4. Exploratory Endpoint Analysis

9.3.4.1. Analyses for Coproporphyrin I

The effect of a single dose of selpercatinib (Day 5) on plasma coproporphyrin I, a biomarker of OATP inhibition in healthy participants, will be explored.

Plasma concentrations of coproporphyrin I will be characterized by standard noncompartmental methods of analysis. Descriptive parameters, such as C_{max}, t_{max}, and area under the concentration versus time curve from time zero to 24 hours (AUC_{0-24}), will be summarized, if feasible.

Pharmacokinetic parameters for coproporphyrin I at the presence of rosuvastatin dosed on Day 1 will be compared to parameters for coproporphyrin I with single dose of selpercatinib dosed on Day 5.

If a participant has an AE of vomiting that occurs at or before 2 times median t_{max} of selpercatinib, the impacted period of this participant will be excluded from the summary statistics and statistical analysis.

9.3.4.2. Statistical Evaluation

Log-transformed C_{max} and AUC_{0-24} of coproporphyrin I will be evaluated in a linear mixed-effects model with fixed effects 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% CIs. The test treatment is coproporphyrin I in the presence of selpercatinib, and reference treatment is coproporphyrin I alone.

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

Approximately 28 participants will be enrolled to ensure that at least 20 evaluable participants complete the study.

A total of 20 evaluable participants will provide at least 90% coverage probability to ensure the half-width of the 90% CI for the AUC ratio of rosuvastatin falls within 25% of the true ratio ([rosuvastatin + selpercatinib] / rosuvastatin). Participants are evaluable if adequate PK data are obtained sufficient for inclusion of the participant in this analysis of AUC ratio. This sample size of at least 20 evaluable participants (out of 28 treated) assumes unknown selpercatinib effect on rosuvastatin PK and intra-participant coefficient of variation of 33% for the PK parameter of interest for each treatment (precision method) based on internal data.

10. Supporting Documentation and Operational Considerations

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

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
  - Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (for example, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for 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
  - Reporting to the sponsor or designee significant issues related to participant safety, participant rights, or data integrity
- Investigator sites are compensated for participation in the study as detailed in the clinical trial agreement.

10.1.2. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

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

10.1.4. 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.

10.1.5. Dissemination of Clinical Study Data

Communication of Suspended or Terminated Dosing

If a decision is taken to suspend or terminate dosing in the trial 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.

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

Data

The sponsor does not proactively share data from Phase 1 clinical trials. Requests for access to Phase 1 clinical trial 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.

10.1.6. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRFs unless transmitted to the sponsor or designee electronically (for example, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF. This might include laboratory tests, medical records, and clinical notes.
- The investigator must review and confirm that data entries are accurate and complete throughout the duration of the study, by physically or electronically signing the CRF, as instructed by the sponsor. All completed CRFs must be signed prior to archival.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source 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 (for example, contract research organizations).
- The sponsor or designee will perform monitoring to confirm that data transcribed into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for the time period outlined in the Clinical Trial Agreement (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, 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 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 (EDC) will be used in this study for the collection of CRF data. The investigator maintains a separate source for the data entered by the investigator or designee into the sponsor-provided EDC system. The investigator is responsible for the identification of any data to be considered source and for the confirmation that data reported are accurate and complete by signing the CRF.

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

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

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

10.1.7. 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 10.1.7.

10.1.8. 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 or sponsor's designee reserves the right to terminate the study at any time for any reason at the sole discretion of the sponsor. Study site 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

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.

10.1.9. 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.

10.1.10. Investigator Information

Not applicable.

10.1.11. Sample Retention

Sample retention enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in the development of selpercatinib or after selpercatinib become(s) commercially available.

Sample Type	**Custodian**	**Retention Period After Last Patient Visit***
Long-term storage samples	Sponsor or Designee	15 years
Pharmacokinetic	Sponsor or Designee	1 year
Genetics	Sponsor or Designee	15 years

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	Sodium
Hemoglobin	Potassium
Erythrocyte count (RBC)	Calcium
Mean cell volume	Phosphorus
Mean cell hemoglobin	Glucose (random)
Mean cell hemoglobin concentration	Creatine kinase
Leukocytes (WBC)	Blood urea nitrogen (BUN)
Platelets	Uric acid
Differential WBC (absolute counts) of:	Total protein
Neutrophils	Albumin
Lymphocytes	Total bilirubin
Monocytes	Alkaline phosphatase (ALP)
Eosinophils	Aspartate aminotransferase (AST)
Basophils	Alanine aminotransferase (ALT)
	Creatinine
Urinalysis	
Specific gravity	Pregnancy test
pH	FSH (if applicable)[b]
Protein	Ethanol testing[c]
Glucose	Urine drug screen[c]
Ketones	
Bilirubin	Serology
Urobilinogen	Hepatitis B surface antigen[b]
Leukocytes	Hepatitis C antibody[b,d]
Blood	HIV[b]
Nitrite	
Microscopic examination of sediment[a]	

Abbreviations: FSH = follicle-stimulating hormone; HIV = human immunodeficiency virus.

[a] Test only if dipstick result is abnormal.
[b] Performed at screening only.
[c] Urine drug screen and ethanol (urine or breath) level performed at screening and may be repeated prior to admission to the clinical research unit.
[d] Participants with a positive hepatitis C antibody test result can have a confirmatory hepatitis C RNA test.

10.2.1. Blood Sampling Summary

This table summarizes the approximate number of venipunctures and blood volumes for all blood sampling (screening, safety laboratories, and bioanalytical assays) during the study.

Protocol J2G-MC-JZPB Sampling Summary

Purpose	Blood Volume per Sample (mL)	Number of Blood Samples	Total Volume (mL)
Screening tests[a]	CCI		
Clinical laboratory tests[a]			
Rosuvastatin pharmacokinetics[b]			
Selpercatinib pharmacokinetics[b]			
Coproporphyrin I pharmacokinetics[b]			
Pharmacogenetics			
Total			
Total for clinical purposes [rounded up to nearest 10 mL]			CCI

[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

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 drug-drug interaction.
- Medication error, misuse, or abuse of IMP, including signs, symptoms, or clinical sequelae.
- The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE. Also, lack of efficacy or failure of expected pharmacological action also constitutes an AE or SAE.

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.

10.3.1. Definition of SAE

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

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

- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.2. Definition of Product Complaints

Product Complaint

- A product complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness or performance of a study intervention. When the ability to use the study intervention safely is impacted, the following are also product complaints:
  - Deficiencies in labeling information, and
  - Use errors for device or drug-device combination products due to ergonomic design elements of the product.
- Product complaints related to study interventions used in clinical trials are collected 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 product complaint or problem with the study intervention so that the situation can be assessed.
- An event may meet the definition of both a product complaint and an AE/SAE. In such cases, it should be reported as both a product complaint and as an AE/SAE.

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

AE, SAE, and Product Complaint Recording

- When an AE/SAE/product complaint occurs, it is the responsibility of the investigator to review all documentation (for example, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE/product complaint information in the participant's medical records, in accordance with the investigator's normal clinical practice. AE/SAE information is reported on the appropriate CRF page and product complaint information is reported on the Product Complaint Form.
- Note: An event may meet the definition of both a product complaint and an AE/SAE. In such cases, it should be reported as both a product complaint and as an AE/SAE.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Sponsor or designee in lieu of completion of the CRF page for AE/SAE and the Product Complaint Form for product complaints.
- There may be instances when copies of medical records for certain cases are requested by 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 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 adverse event 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 adverse event 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 adverse event 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 a 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 Investigator's Brochure (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 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 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 Sponsor or designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Sponsor or designee with a copy of any postmortem findings including histopathology.

10.3.4. Reporting of SAEs

SAE Reporting via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the SAE paper form (see next section) in order to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a SAE paper form (see next section) or to the sponsor or designee by telephone.
- Contacts for SAE reporting can be found in SAE Report.

SAE Reporting via Paper Form

- Facsimile transmission of the SAE paper form 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 CRF pages within the designated reporting time frames.
- Contacts for SAE reporting can be found in in SAE Report.

10.3.5. 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, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (for example, summary or listing of SAEs) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Definitions

Word/Phrase	Definition
Women of childbearing potential (WOCBP)	Adult females are considered WOCBP unless they are WNOCBP. Females less than 18 years of age are considered WOCBP if they have • had at least 1 cycle of menses, or • Tanner stage 4 breast development. Any amount of spotting should be considered menarche.
Women not of childbearing potential (WNOCBP)	Females are considered WNOCBP if they • have a congenital anomaly such as Müllerian agenesis • are infertile due to surgical sterilization, or • are postmenopausal. Examples of surgical sterilization include total hysterectomy, bilateral salpingo-oophorectomy, bilateral salpingectomy, or bilateral oophorectomy.
Postmenopausal state	The postmenopausal state is defined as a woman: • at any age at least 6 weeks post-surgical bilateral oophorectomy with or without hysterectomy, confirmed by operative note; or • aged at least 40 years and up to 55 years with an intact uterus, not on hormone therapy[a], 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 • 55 years or older not on hormone therapy, who has had at least 12 months of spontaneous amenorrhea, or • aged at least 55 years with a diagnosis of menopause prior to starting hormone replacement therapy.

a Women 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

Male participants:

- Are not required to adhere to contraceptive requirements.

Female participants:

- WNOCBP are not required to adhere to contraceptive requirements. This includes females who are:
  - Infertile due to surgical sterilization (hysterectomy, bilateral oophorectomy, bilateral salpingectomy, bilateral tubal occlusion, or bilateral tubal ligation), or congenital anomaly (for example, Müllerian agenesis)
  - Postmenopausal

WOCBP who are completely abstinent as their preferred and usual lifestyle, or in a same-sex relationship as their preferred and usual lifestyle:

Must…	Must not…
agree to either remain abstinent or stay in a same-sex relationship without sexual relationships with males	• use periodic abstinence methods ○ calendar ○ ovulation ○ symptothermal, or ○ post-ovulation • declare abstinence just for the duration of a trial, or • use the withdrawal method

WOCBP who are NOT completely abstinent as their preferred and usual lifestyle, or NOT in a same-sex relationship as their preferred and usual lifestyle, must do the following:

Topic	Condition
Pregnancy testing	Have a negative serum test result at screening followed by a negative urine result within 24 hours prior to treatment exposure. See the protocol Schedule of Activities for subsequent pregnancy testing requirements.
Contraception	Agree to use 2 forms of effective contraception, where at least 1 form must be highly effective.
	These forms of contraception must be used during the study and after the study for at least 30 days after the last dose of the study intervention.

10.4.3. Contraception Methods

The table illustrates examples of highly effective, effective, and unacceptable methods of contraception.

Methods	Examples
Highly effective contraception (less than 1% failure rate)	• female sterilization • combination oral contraceptive pill • progestin-only contraceptive pill (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

Ineffective forms of contraception whether used alone or in any combination	• spermicide alone • periodic abstinence • fertility awareness (calendar method, temperature method, cervical mucus, or symptothermal) • withdrawal • postcoital douche, or • lactational amenorrhea

10.5. Appendix 5: Genetics

Use/Analysis of DNA

- Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Variable response to study intervention may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting participants.
- DNA samples will be used for research related to selpercatinib or cancer and related diseases. They may also be used to develop tests/assays including diagnostic tests related to selpercatinib and/or interventions of this drug class and cancer. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome or analysis of the entire genome (as appropriate).
- Additional analyses may be conducted if it is hypothesized that this may help further understand the clinical data.
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to selpercatinib or study interventions of this class to understand study disease or related conditions.
- The results of genetic analyses may be reported in the clinical study report (CSR) or in a separate study summary.
- The sponsor will store the blood and/or DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on selpercatinib or study interventions of this class or indication continues but no longer than 15 years or other period as per local requirements.

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

See Section 8.2.6.1 for guidance on appropriate test selection.

The Lilly-designated central laboratory should complete the analysis of all selected testing. The central laboratory will report results if a validated test or calculation is available.

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

Abbreviations: Ig = immunoglobulin; INR = international normalized ratio; PT-INR = prothrombin time-international normalized ratio.

[a] Not required if anti-actin antibody is tested.

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

[c] Not required if anti-smooth muscle antibody (ASMA) is tested.

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

Not applicable.

10.8. Appendix 8: Abbreviations and Definitions

Term	Definition
ab	antibody
abuse	Use of a study intervention for recreational purposes or to maintain an addiction or dependence
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
$AUC_{(0-\infty)}$	area under the concentration versus time curve from time zero to infinity
$AUC_{(0-24)}$	area under the concentration versus time curve from time zero to 24 hours
$AUC_{(0-tlast)}$	area under the concentration versus time curve from time zero to time t, where t is the last time point with a measurable concentration
BCRP	breast cancer resistance protein
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.
COVID-19	coronavirus disease 2019
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 trial 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
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 informed consent form directly or through their legally acceptable representatives.
FDA	Food and Drug Administration
GCP	good clinical practice
HBV	hepatitis B virus
HCV	hepatitis C virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee
IMP	Investigational Medicinal Product (see also "investigational product") A medicinal product which is being tested or used as a reference, including as a placebo, in a clinical trial.
informed consent	A process by which a participant voluntarily confirms their willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the participant's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form. See also "IMP."
OATP1B1	organic anion transporting polypeptide 1B1
participant	Equivalent to CDISC term "subject": an individual who participates in a clinical trial, either as recipient of an investigational medicinal product or as a control
PC	product complaint
PK	pharmacokinetics
QTc	corrected QT interval
QTcB	QT corrected using Bazett's formula
QTcF	QT corrected using Fridericia's formula
SAE	serious adverse event

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 elimination 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

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