Protocol J2G-MC-JZPA

An Open-Label, Randomized, Two-Period Crossover Study to Investigate the Effect of Food on the Pharmacokinetics of Selpercatinib in Healthy Participants

NCT05324124

Approval Date: 22-Nov-2021

Title Page

Protocol Title: An Open-Label, Randomized, Two-Period Crossover Study to Investigate the Effect of Food on the Pharmacokinetics of Selpercatinib in Healthy Participants

Protocol Number: J2G-MC-JZPA

Amendment Number: This is the initial protocol.

Compound: LY3527723 (selpercatinib)

Brief Title: A Food-Effect Study of Selpercatinib in Healthy Participants

Study Phase: 1

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

Legal Registered Address: Indianapolis, Indiana 46285 USA

Regulatory Agency Identifier Number:

IND: 133193

Approval Date: Protocol Electronically Signed and Approved by Lilly on date provided below.

Approval Date: 22-Nov-2021 GMT

Medical Monitor Name and Contact Information will be provided separately.

Table of Contents

1. Protocol Summary

1.1. Synopsis

Protocol Title: An Open-Label Study to Investigate the Effect of Food on the Pharmacokinetics of Selpercatinib in Healthy Participants

Brief Title: A Food-Effect Study of Selpercatinib in Healthy Participants

Rationale:

This clinical study is being conducted to assess the effect of food on the new tablet formulation of selpercatinib at the highest unit strength. Two single doses of 160 mg selpercatinib will be administered in this study, which is supported by the available safety data and is the clinically recommended dose.

A previous study (LOXO-RET-18015) evaluated the effect of food and the effect of a PPI on the single-dose PK of selpercatinib at the clinically recommended dose of 160 mg. Exposures to selpercatinib under fed conditions were similar to exposures under fasting conditions. Under fasting conditions, coadministration of omeprazole reduced the exposure of selpercatinib (C_{max} and AUC) by 88% and 69%, respectively. These results are consistent with the pH-dependent solubility of selpercatinib.

No clinically significant differences in selpercatinib AUC or C_{max} were observed following administration of a low-fat or high-fat meal (approximately 900 calories, 58 grams carbohydrate, 56 grams fat and 43 grams protein) in healthy participants.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
To assess the effect of food on the PK of selpercatinib after a high-fat meal in healthy participants	$AUC_{0-\infty}$, AUC_{tlast}, and C_{max} of selpercatinib
Secondary	
To assess the safety and tolerability of 160 mg of selpercatinib	Summary of the number of treatment-emergent AEs and serious AEs

Overall Design:

The anticipated study duration for each individual participant is approximately 7 weeks.

Screening

All participants will be screened within 28 days prior to enrollment (Day 1).

Treatment and Assessment Period

Eligible participants will take part in 1 treatment period. Participants will be admitted to the CRU on Day -1. All participants will be randomized to receive either a single dose of 160 mg selpercatinib in the fasted or fed state on Day 1, and will have the alternate treatment (i.e., fasted or fed, per the randomization schedule) on Day 8.

Participants will remain resident at the CRU until Day 11. A study participant may be required to stay later than Day 11 for management or monitoring of an AE or a clinically significant finding, at the discretion of the investigator.

There will be a washout period of 7 days between dosing on Days 1 and 8.

PK blood sampling and safety assessments, including vital signs measurements, physical examinations, clinical laboratory tests, electrocardiograms, and AE recording, will be performed.

Follow-up

Participants will receive a follow-up phone call 7 to 10 days after the last dose of selpercatinib.

Number of Participants:

Approximately 46 participants will be enrolled to ensure that at least 38 evaluable participants complete the study.

Intervention Groups and Duration:

This is a single-group study, consisting of single oral doses of selpercatinib on Days 1 and 8.

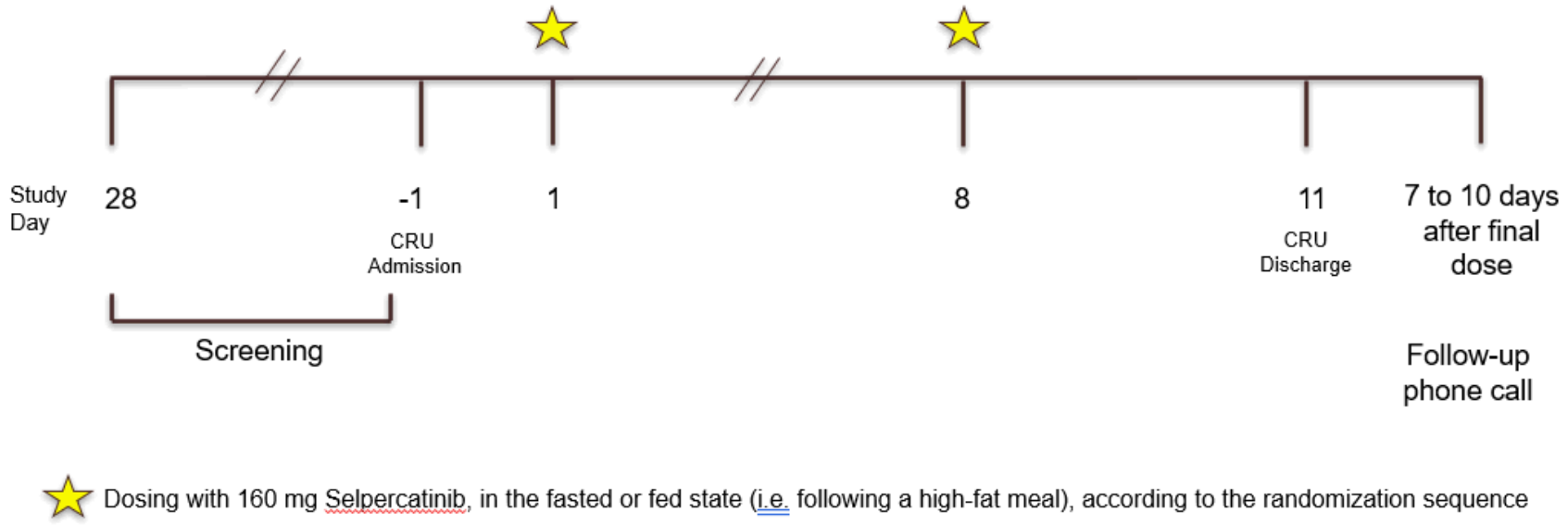
All participants will be randomized to receive either a single oral dose of selpercatinib 160 mg will be administered in the morning of Day 1 in the fasted or fed state, and will have the alternate treatment (i.e. fasted or fed, per the randomization schedule) on Day 8. Both doses of selpercatinib will be administered with approximately 240 mL of room temperature water while in a sitting position. Participants will not be allowed to lie supine for 2 hours after dosing, unless clinically indicted or for study procedures.

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

The high-fat breakfast (fat comprises approximately 50% of total calorific content) should consist of approximately 800 to 1000 calories in total. No additional food or substitute is allowed. The test meal derives approximately 150, 250, and 500 to 600 calories from protein, carbohydrate, and fat, respectively.

Data Monitoring Committee: No

1.2. Schema



Abbreviations: CRU = clinical research unit.

1.3. Schedule of Activities (SoA)

	Screening	**Treatment Period**													**Follow-Up phone call**	**Comments**
		Days														
Procedure	-28 to -2 days prior to Day 1	-1	1	2	3	4	5	6	7	8	9	10	11	**ED**	**within 7 to 10 days after last dose**	
Informed consent	X															
Inclusion and exclusion criteria	X															
Demography	X															
Participant admission to CRU		X														
Participant discharge from CRU													X			A study participant may be required to stay later than Day 11 for management or monitoring of an AE or a clinically significant finding, at the discretion of the investigator.
Outpatient visit	X															

	Screening	**Treatment Period**												**Follow-Up phone call**	**Comments**
		Days													
Procedure	-28 to -2 days prior to Day 1	-1	1	2	3	4	5	6	7	8	9	10	11	**ED**	**within 7 to 10 days after last dose**	
Medical history	X															
Medical assessment	X		P							P			X	X		Full medical assessment to be performed at screening, and symptom driven examination to be done at other/any time point at physician's discretion.
Height and weight	X												X	X		Height and weight to be measured at screening; weight only to be measured at Day 11 or ED as appropriate.

	Screening	**Treatment Period**												**Follow-Up phone call**	**Comments**
		Days													
Procedure	-28 to -2 days prior to Day 1	-1	1	2	3	4	5	6	7	8	9	10	11	**ED**	**within 7 to 10 days after last dose**	
Serum or urine pregnancy test (women of childbearing potential only)	X	X											X	X		Serum pregnancy tests will be performed at screening and urine pregnancy test at all other time points
Follicle-stimulating hormone (women of non-childbearing potential only)	X															
Human immunodeficiency virus, hepatitis B and C screen	X															
12-lead ECG	X		P, 2h		X					P, 2h		X	X	X		Single ECGs are required.
Vital signs (supine), pulse rate, and blood pressure	X		P, 1, 2h	24h	X	X				P, 1,2h	24h	X	X	X		Time points may be added, if warranted and agreed upon between Lilly and the investigator.
Clinical laboratory tests	X		P	24h		X				P	24h		X	X		See Appendix 10.2, Clinical Laboratory Tests, for details.

	Screening	Treatment Period													Follow-Up phone call	Comments
		Days														
Procedure	-28 to -2 days prior to Day 1	-1	1	2	3	4	5	6	7	8	9	10	11	**ED**	**within 7 to 10 days after last dose**	
Genetic sample			X													
CCI																
Selpercatinib administration			X							X						Participant consumes high-fat meal within 30 minutes prior to dose based on randomization.
Adverse event /Serious adverse event review	X	X	←═══════════════════════════→											X		
Concomitant medication review	X	X	←═══════════════════════════→											X		

Abbreviations: CRU = clinical research unit; ECG = electrocardiogram; ED = early discontinuation; h = hour; CCI

2. Introduction

Selpercatinib has been developed by Loxo Oncology, Inc. and acquired by Eli Lilly and Company (Lilly), and has been approved by the FDA for the treatment of advanced or metastatic RET-mutant MTC, and advanced or metastatic RET fusion-positive thyroid cancer, in adults and children ≥12 years; and for the acute treatment of metastatic RET fusion-positive NSCLC in adults.

Full details of the preclinical and clinical safety and tolerability data are contained in the IB.

2.1. Study Rationale

Lilly is developing a tablet formulation in strengths of 40 mg, 80 mg, 120 mg, and 160 mg that will replace the current commercial capsule formulation. The tablets are intended to offer an improved patient experience in terms of the number and size of the dosage units.

This clinical study is being conducted to assess the effect of food on the new tablet formulation of selpercatinib at the highest unit strength. Two single doses of 160 mg selpercatinib will be administered in this study, which is supported by the available safety data and is the clinically recommended dose.

A previous study (LOXO-RET-18015) evaluated the effect of food and the effect of a PPI on the single-dose PK of the selpercatinib commercial capsule formulation at the clinically recommended dose of 160 mg. Exposures to selpercatinib under fed conditions were similar to exposures under fasting conditions. Under fasting conditions, coadministration of omeprazole reduced the exposure of selpercatinib (C_{max} and AUC) by 88% and 69%, respectively. These results are consistent with the pH-dependent solubility of selpercatinib.

No clinically significant differences in selpercatinib AUC or C_{max} were observed following administration of a low-fat or high-fat meal (approximately 900 calories, 58 grams carbohydrate, 56 grams fat and 43 grams protein) in healthy subjects.

2.2. Background

Selpercatinib (LY3527723) is a highly potent and specific small-molecule inhibitor of the RET kinase, with minimal inhibition of other kinase and nonkinase targets. The approved dosing regimen is 120 mg orally twice daily (in patients <50 kg) and 160 mg orally twice daily (in patients ≥50 kg).

Selpercatinib doses have been evaluated in healthy participants or patients with advanced or metastatic RET-mutant, advanced or metastatic RET fusion-positive thyroid cancer, and metastatic RET fusion-positive NSCLC across Phase 1, 2, and 3 clinical studies. Across these studies, single oral doses of selpercatinib were administered over a range of 20 to 720 mg.

In previous 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. The most frequently reported (≥15% of participants regardless or attribution to study drug) AEs in the ongoing studies were dry mouth, diarrhea, hypertension, AST/ALT increased, abdominal pain, rash, ECG QT prolonged, cough, vomiting, and dyspnea.

In the absence of acid-reducing agents, there is little effect of food on the PK of selpercatinib. Following dosing with 160 mg selpercatinib (2 × 80 mg) in the commercial capsule formulation, a high-fat breakfast resulted in an increase of approximately 9% in selpercatinib AUC and an approximately 14% decrease in the C_{max} compared to fasting conditions.

In healthy participants the median (range) t_{max} of selpercatinib is 2 (1.5 to 6.0) hours and is eliminated with a mean (range) $t_{1/2}$ 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 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 dose of selpercatinib to be given in this study is 160 mg, as it is the highest approved dose by the FDA. The safety profile of selpercatinib is very well tolerated in healthy participants and is clinically manageable, with low rates of study drug discontinuation due to 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, AST/ALT elevation, headache, nausea, edema peripheral, abdominal pain, rash, ECG QT prolonged, cough, vomiting, dyspnea and increased blood creatinine. Events of special interest include hypersensitivity, liver-function test abnormalities, thrombocytopenia, and hypertension. In a recently completed study in healthy participants (J2G-MC-JZJV), only 1 TEAE considered to be related to selpercatinib was reported (dyspepsia).

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

3. Objectives and Endpoints

Objectives	Endpoints
Primary	
To assess the effect of food on the PK of selpercatinib after a high-fat meal in healthy participants	$AUC_{0-\infty}$, AUC_{tlast}, and C_{max} of selpercatinib
Secondary	
To assess the safety and tolerability of 160 mg of selpercatinib	Summary of the number of treatment-emergent AEs and SAEs

4. Study Design

4.1. Overall Design

This is a Phase 1, open-label, randomized, 2-period, 2-sequence crossover study of the PK of selpercatinib in the fed and fasted state. The anticipated study duration for each individual participant is up to approximately 7 weeks.

Screening

All participants will be screened within 28 days prior to enrollment (Day 1).

Treatment and Assessment Period

Eligible participants will take part in 1 treatment period. Participants will be admitted to the CRU on Day -1. All participants will be randomized to receive either a single dose of 160 mg selpercatinib in the fasted or fed state on Day 1, and will have the alternate treatment (i.e., fasted or fed, per the randomization schedule) on Day 8.

Participants will remain resident at the CRU until Day 11. A study participant may be required to stay later than Day 11 for management or monitoring of an AE or a clinically significant finding, at the discretion of the investigator.

There will be a washout period of 7 days between dosing on Days 1 and 8. The doses will be administered at approximately the same times on Days 1 and 8. The actual time of dose administrations will be recorded in the participant's eCRF.

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

Follow-up

Participants will receive a follow-up phone call 7 to 10 days after the last dose of selpercatinib.

4.2. Scientific Rationale for Study Design

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 selpercatinib of approximately 14 hours in healthy participants, a period of 7 days between selpercatinib doses is considered sufficient time for the study drug to washout.

A randomized, 2-period crossover design will be used so that each participant serves as his/her own control.

Conducting the study in healthy participants mitigates the potential confounding effects of the disease state and concomitant medications in participants with metastatic RET fusion-positive NSCLC, advanced or metastatic RET-mutant MTC, or advanced or metastatic RET fusion-positive thyroid cancer. A population of healthy participants is frequently used in the assessment of the PK of both small and large molecules.

4.3. Justification for Dose

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

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all required phases of the study including the last visit or the last scheduled procedure shown in the SoA, follow up phone call.

The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in the SoA for the last participant in the study.

5. Study Population

Eligibility of participants for enrollment in the study will be based on the results of screening medical history, physical examination, vital signs, clinical laboratory tests, and ECG.

The inclusion and exclusion criteria used to determine eligibility should be applied at screening only, and not continuously throughout the study. Clinical laboratory assessments 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 28 days prior to enrollment. Participants who are not enrolled within 28 days of screening may undergo an additional medical assessment and/or clinical measurements to confirm their eligibility. In such instances, the following screening tests and procedures should be repeated: clinical laboratory assessments and vital signs.

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 21 to 65 years of age inclusive, at the time of signing the ICF.

Type of Participant

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

Weight

5. Have a body mass index within the range 18.5 to 35.0 kg/m^2 (inclusive)

Sex and Contraceptive/Barrier Requirements

6. Male or female

Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies

a) Male participants:
   - may participate in this study

Female participants:
   - of childbearing potential may participate in this study

- not of childbearing potential may participate in this study

Please refer to Section 10.4 for definitions and additional guidance related to contraception.

Informed Consent

7. Capable of giving signed informed consent as described in Appendix 1 (Section 10.1.2), which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

5.2. Exclusion Criteria

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

Medical Conditions

1. Have a positive pregnancy test at screening or Day -1, where applicable
2. Are planning to become pregnant during the study or within 1 month of study completion
3. Are women who are lactating
4. Have known allergies to selpercatinib, selpercatinib-related compounds or any components of the formulation of selpercatinib, or history of significant atopy
5. Have a history of allergic reactions to medications or food products
6. Have a clinically significant abnormality of blood pressure and/or pulse rate as determined by the investigator
7. Have an abnormality in the 12-lead ECG that, in the opinion of the investigator, increases the risks associated with participating in the study or may confound ECG data analysis, including prolongation of the QTcB or QTcF >450 msec at screening
8. Have clinically significant active cardiovascular disease or history of myocardial infarction within 6 months prior to the planned start of selpercatinib
9. Have a 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. Appendectomy, and splenectomy, are considered as acceptable
10. 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
11. Have a history or presence of neuropsychiatric disease (e.g., bipolar disorder, schizophrenia, depression) considered as clinically significant by the investigator
12. Participants who show evidence of HIV infection and/or positive HIV antibodies. A negative test within 6 months of screening would not need to be repeated
13. Participants who show evidence of positive hepatitis B surface antigen. A negative test within 6 months of screening would not need to be repeated
14. Participants who show evidence of positive hepatitis C antibody. A negative test within 6 months of screening would not need to be repeated. Participants with a positive hepatitis C antibody test result can have a confirmatory hepatitis C RNA test.

15. Have donated blood of more than 450 mL or have participated in a clinical study that required similar blood volume drawn within the past 3 calendar months of study screening
16. Have any medical conditions, medical history, or are taking any medications which are contraindicated in the selpercatinib label
17. Have had lymphoma, leukemia, or any malignancy within the past 5 years except for basal cell or squamous epithelial carcinomas of the skin that have been resected with no evidence of metastatic disease for 3 years

Prior/Concomitant Therapy

18. Have participated, within the last 30 days or 5 half-lives (whichever is longer) of admission, in a clinical study involving an investigational product.
19. Have previously completed or withdrawn from this study or any other study investigating selpercatinib, and have previously received the investigational product
20. Use of H_2 blockers, proton pump inhibitors, and other drugs that affect selpercatinib exposure within 7 days of screening
21. Are intending to use over-the-counter or prescription medication, including dietary supplements, 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

22. 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

Other Exclusions

23. Have an average weekly alcohol intake that exceeds 21 units per week (males) and 14 units per week (females); 1 unit = 12 oz or 360 mL of beer; 5 oz or 150 mL of wine; 1.5 oz or 45 mL of distilled spirit(s)
24. Are unwilling to stop alcohol consumption 24 hours prior to each 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
25. Are unwilling to abstain from ingesting caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks, and chocolate) for 24 hours prior to each admission until after discharge from the CRU
26. Are unable to refrain from smoking while resident at the CRU
27. Have used or intend to use any medications/products known to alter drug absorption, metabolism, or elimination processes, within 30 days (or 5 half-lives, whichever is longest) prior to check-in, unless deemed acceptable by the investigator. All inhibitors/inducers of CYP3A4 are specifically excluded.
28. Are unable to consume a standardized meal within the required time frame

29. 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
30. Are Lilly employees or are an employee of any third-party involved in the study who require exclusion of their employees
31. 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
32. In the opinion of the investigator or sponsor, are unsuitable for inclusion in the study.

5.2.1. Meals and Dietary Restrictions

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

On fed dosing days, participants will receive a high-fat meal as outlined in Section 6.1.1.

No additional food should be allowed for at least 4 hours after drug administration.

5.2.2. Substance Use: Caffeine, Alcohol, and Tobacco

Participants will abstain from ingesting caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks, and chocolate) for 24 hours prior to each admission until after discharge from the CRU, where applicable.

Participants will abstain from alcohol for 24 hours prior to each admission until after discharge from the CRU, where applicable.

Participants who use tobacco products will be instructed that use of nicotine-containing products (including nicotine patches) will not be permitted while they are in the CRU.

5.2.3. Activity

Participants will abstain from strenuous exercise during study participation.

5.3. Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened. Repeating of laboratory tests during the screening period or repeating screening tests to comply with the protocol designated screening period does not constitute rescreening.

6. Study Intervention(s) and Concomitant Therapy

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

6.1. Study Intervention Administered

Table JZPA.1. Study Interventions Administered

Study Intervention	Selpercatinib
Dosage Formulation	Tablet
Unit Dose Strength/Dosage Level	1 × 160-mg tablets (160 mg selpercatinib)
Route of Administration	Oral
Dosing Instructions	1 tablet taken on Days 1 and 8

6.1.1. Administration Details

A single oral dose of selpercatinib 160 mg will be administered in the morning of Days 1 and 8 in the fasted or fed state (i.e., following consumption of a high fat meal), according to the randomization sequence.

On dosing days, participants will be fasted overnight (at least 10 hours) prior to dosing. No additional food should be allowed for at least 4 hours after drug administration.

On fed dosing days, participants will be dosed following consumption of a high fat meal. The participants will complete the high-fat meal 30 minutes prior to administration of study intervention (i.e., participants will be dosed 30 minutes after the start of the meal), and participants should eat this meal in 30 minutes or less. If participants take lesser time to eat, dosing will still occur at 30 minutes after the reference time.

The high-fat breakfast (fat comprises approximately 50% of total calorific content) should consist of approximately 800 to 1000 calories in total. No additional food or substitute is allowed. An example of a typical test meal is provided in Appendix 7 (Section 10.7). The test meal derives approximately 150, 250, and 500 to 600 calories from protein, carbohydrate, and fat, respectively.

Participants will be encouraged to eat the full meal. Each component of the meal will be weighed separately and documented in grams pre and post meal to determine the percentage of the meal consumed in grams by the participant. The nutritional intake will be documented in grams and recorded in the eCRF.

Both doses of selpercatinib will be administered with approximately 240 mL of room temperature water while in a sitting position. Participants will not be allowed to lie supine for 2 hours after dosing, unless clinically indicted or for study procedures.

On all dosing occasions, participants will refrain from consuming water from 1 hour predose until 2 hours postdose, excluding the amount of water consumed at dosing. At all other times during the study, participants may consume water ad libitum.

Selpercatinib tablets should be swallowed whole. Participants should not break or chew either tablet.

On non-dosing days, participants will adhere to meal restrictions as outlined in Section 5.2.1.

6.2. Preparation, Handling, Storage, and Accountability

1. The investigator or designee must confirm appropriate storage conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention. Only authorized study personnel may supply, prepare, or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized study personnel.
3. The investigator or authorized study personnel are responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
4. The investigator or designee will return all unused study interventions to Lilly or its designee at the end of the study. In some cases, sites may destroy the material if, during the CRU selection, the evaluator has verified and documented that the site has appropriate facilities and written procedures to dispose of clinical materials.

6.3. Measures to Minimize Bias: Randomization and Blinding

This is an open-label study. There is no bias as the primary endpoint is PK and objective in measure.

6.4. Study Intervention Compliance

Participants are dosed at the site and will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the eCRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention. Study site personnel will examine each participant's mouth to ensure that the study intervention was ingested.

6.5. Dose Modification

Dose modification is not permitted in this study.

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

Not applicable.

6.7. Treatment of Overdose

For the purposes of this study, an overdose of selpercatinib is considered as any dose higher than the dose assigned. There is no specific antidote for selpercatinib.

In the event of an overdose, the investigator/treating physician should:

- Contact the medical monitor immediately.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities until study intervention can no longer be detected systemically (at least 5 days).
- Document the quantity of the excess dose as well as the duration of the overdose in the eCRF.

6.8. 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 over-the-counter or prescription medication, including dietary supplements, within 14 days before the start of study intervention until discharge from the study.

Acetaminophen, at doses of ≤3 grams/24 hours, is permitted for use at the discretion of the investigator for the treatment of headache, etc. 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 CP/CRP, or designee.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

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

7.1. Discontinuation of Study Intervention

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

7.1.1. Liver Chemistry Stopping Criteria

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

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

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

Liver Safety: Suggested Actions and Follow-up Assessments can be found in Appendix 6 (Section 10.6).

7.1.2. QTc Stopping Criteria

A participant who meets either bulleted criterion following single ECG assessment should have ECG repeated. If the participant still meets either bulleted criterion they may be withdrawn from the study.

- QTc, QTcB, QTcF >500 msec
- Change from baseline in QTc >60 msec.

If a clinically significant finding is identified (including, but not limited to changes from baseline in QTcB or QTcF) after enrollment, the investigator or qualified designee will determine if the participant can continue in the study 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.

See the SoA for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed.

7.2. Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the study:

- at any time at the participant's own request
- at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons
- if the participant becomes pregnant during the study
- if enrollment in any other clinical study involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study.

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

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

7.2.1. Discontinuation of Inadvertently Enrolled Participants

If the sponsor or investigator identify a participant who did not meet enrollment criteria and was inadvertently enrolled, then the participant should be discontinued from study treatment unless there are extenuating circumstances that make it medically necessary for the participant to continue on study treatment. If the investigator and the sponsor CRP agree it is medically appropriate to continue, the investigator must obtain documented approval from the sponsor CRP to allow the inadvertently enrolled participant to continue in the study with or without treatment

with investigational product. Safety follow-up is as outlined in the SoA (Section 1.3), Section 8.2 (Safety Assessments), and Section 8.3 (Adverse Events, Serious Adverse Events, and Product Complaints) of the protocol.

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.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1 (Section 10.1).

8. Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA (Section 1.3).
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

The specifications in this protocol for the timings of safety and sample collection are given as targets to be achieved within reasonable limits. Modifications may be made to the time points based upon emerging clinical information. The scheduled time points may be subject to minor alterations; however, the actual time has to be correctly recorded in the CRF. Failure or being late (i.e., outside stipulated time allowances) to perform procedures or obtain samples due to legitimate clinical issues (e.g., equipment technical problems, venous access difficulty, or subject defaulting or turning up late on an agreed scheduled procedure) will not be considered as protocol deviations but the CRU will still be required to notify the sponsor in writing via a file note.

8.1. Efficacy Assessments

Not applicable.

8.2. Safety Assessments

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

8.2.1. Medical Assessment

A complete medical assessment will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems. Height and weight will also be measured and recorded.

A symptom driven examination may be done at other/any time point at physician's discretion

8.2.2. Vital Signs

- Blood pressure and pulse rate should be measured singly after at least 5 minutes supine. For each individual participant, the same cuff size should be used throughout the study for the measurements of blood pressure. The cuff should be attached to the participant's dominant arm, where possible.
- Unscheduled orthostatic vital signs should be assessed, if possible, during any AE of dizziness or posture induced symptoms. Where orthostatic measurements are required,

participants should be supine for at least 5 minutes and then participants will stand, and standing blood pressure will be measured after 2 minutes, but no longer than 3 minutes. If the participant feels unable to stand, supine vital signs only will be collected. Additional vital signs may be measured if warranted.

8.2.3. Electrocardiograms

- Refer to Section 7 for QTc withdrawal criteria and any additional QTc readings that may be necessary.
- ECGs must be recorded before collecting any blood samples. Participants must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection. ECGs may be obtained at additional times, when deemed clinically necessary. All ECGs recorded should be stored at the investigational site.
- ECGs will be interpreted by the investigator at the site as soon after the time of ECG collection as possible, and ideally while the participant is still present, to determine whether the participant meets 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 baselined) 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

- The investigator must review the laboratory results, document this review, and report any clinically relevant changes occurring during the study as an AE. The laboratory results must be retained with source documents unless a Source Document Agreement or comparable document cites an electronic location that accommodates the expected retention duration. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or 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 (Section 10.2), must be conducted in accordance with the SoA (Section 1.3), standard collection requirements, and laboratory manual.

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

8.2.5. Safety Monitoring

The Lilly CP or CRP/scientist will monitor safety data throughout the course of the study.

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

- trends in safety data
- laboratory analytes including hematology and chemistry.

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

8.2.5.1. Hepatic Safety

Close hepatic monitoring

Laboratory tests (Appendix 6 [Section 10.6]), including ALT, AST, ALP, TBL, D. Bil, GGT, and CK, should be repeated within 48 to 72 hours to confirm the abnormality and to determine if it is increasing or decreasing, if one or more of these conditions occur:

If a participant with baseline results of...	develops the following elevations:
ALT or AST <1.5x ULN	ALT or AST ≥3x ULN
ALP <1.5x ULN	ALP ≥2x ULN
TBL <1.5x ULN	TBL ≥2x ULN (except for patients with Gilbert's syndrome)
ALT or AST ≥1.5x ULN	ALT or AST ≥2x baseline
ALP ≥1.5x ULN	ALP ≥2x baseline
TBL ≥1.5x ULN	TBL ≥1.5x baseline (except for patients with Gilbert's syndrome)

If the abnormality persists or worsens, clinical and laboratory monitoring, and evaluation for possible causes of abnormal liver tests should be initiated by the investigator in consultation with the Lilly-designated medical monitor. At a minimum, this evaluation should include medical assessment 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 lab results stabilize. Monitoring of ALT, AST, ALP, and TBL should continue until levels normalize or return to approximate baseline levels.

Comprehensive hepatic evaluation

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

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

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

At a minimum, this evaluation should include physical examination and a thorough medical history, as outlined above, as well as tests for PT-INR; tests for viral hepatitis A, B, C, or E; tests for autoimmune hepatitis; and an abdominal imaging study (for example, ultrasound or CT 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 (HDV), cytomegalovirus (CMV), Epstein-Barr virus (EBV), 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 (MRCP), endoscopic retrograde cholangiopancreatography (ERCP), 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 ≥5x ULN on 2 or more consecutive blood tests (if baseline ALT <1.5x ULN)
   - In participants with baseline ALT ≥1.5x ULN, the threshold is ALT ≥3x baseline on 2 or more consecutive tests

2. Elevated TBL to ≥ 2x ULN (if baseline TBL <1.5x ULN) (except for cases of known Gilbert's syndrome)
   - In participants with baseline TBL ≥1.5x ULN, the threshold should be TBL ≥2x baseline
3. Elevation of serum ALP to ≥2x ULN on 2 or more consecutive blood tests (if baseline ALP <1.5x ULN)
   - In participants with baseline ALP ≥1.5x ULN, the threshold is ALP ≥2x 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.

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

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

- Adverse events (AEs)
- Serious adverse events (SAEs)
- Product complaints (PCs)

These events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

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

8.3.1. Timing and Mechanism for Collecting Events

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

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-up Method of Reporting
Adverse Event					
AE	signing of the ICF	participation in study has ended	as soon as possible upon site awareness	AE CRF	N/A

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-up Method of Reporting
Serious Adverse Event					
SAE and SAE updates – prior to start of study intervention **and** deemed reasonably possibly related with study procedures	signing of the ICF	start of intervention	within 24 hours of awareness	SAE paper form	SAE paper form
SAE and SAE updates – after start of study intervention	start of intervention	participation in study has ended	Within 24 hours of awareness	SAE paper form	SAE paper form
SAE* – after participant's study participation has ended **and** the investigator becomes aware	after participant's study participation has ended	N/A	Promptly	SAE paper form	N/A
Pregnancy					
Pregnancy in female participants and female partners of male participants	after the start of study intervention	at least 5 terminal half-lives or 30 days after the last dose, whichever is longer	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	Product Complaint form	N/A

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-up Method of Reporting
PC not associated with an SAE	Start of study intervention	End of study intervention	Within 1 business day of awareness	Product Complaint form	N/A
Updated PC information	—	—	As soon as possible upon site awareness	Originally completed Product Complaint form with all changes signed and dated by the investigator	N/A
PC (if investigator becomes aware)	Participation in study has ended	N/A	Promptly	Product Complaint form	

* Serious adverse events

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.

Prior to continuation of study intervention following pregnancy, the following must occur:

- The sponsor and the relevant IRB/IEC give written approval.
- The participant gives signed informed consent.
- The investigator agrees to monitor the outcome of the pregnancy and the status of the participant and the participant's offspring.

8.4. Pharmacokinetics

- Plasma samples of approximately 2 mL will be collected for measurement of plasma concentrations of selpercatinib as specified in the SoA (Section 1.3).
- A maximum of 3 samples may be collected at additional time points during the study if warranted and agreed upon between the investigator and the sponsor. The timing of sampling may be altered during the course of the study based on newly available data (e.g., 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.

8.5. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.6. Genetics

A blood sample for DNA isolation will be collected from participants.

See Appendix 5 (Section 10.5) for Information regarding genetic research and Appendix 1 (Section 10.1.6) for details about sample retention and custody.

8.7. Biomarkers

Biomarkers are not evaluated in this study.

8.8. Immunogenicity Assessments

Not applicable for this study.

8.9. Health Economics

Health economics are not evaluated in this study.

9. Statistical Considerations

The statistical analysis plan (SAP) will be finalized prior to first participant first visit, and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses

9.1. Statistical Hypotheses

The primary objective variables will be evaluated to assess the potential food effect on the PK of selpercatinib.

An absence of a food effect on bioavailability will be established if the 90% confidence interval for the ratio of the population geometric means is contained in the equivalence limits of 80 to 125% for AUC values and C_{max}.

9.2. Analyses Sets

The following analysis sets are defined:

Participant Analysis Set	Description
Safety analysis set	All participants who received at least 1 dose of study intervention. Participants will be analyzed according to the intervention they actually received.
Pharmacokinetic analysis set	All participants who received both doses of study intervention 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, and other demographic characteristics will be recorded and summarized. Demographic characteristics may be considered in the interpretation of PK and safety analyses.

9.2.3. Treatment Compliance

The date and time of dosing will be recorded and listed.

9.3. Statistical Analyses

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

Additional exploratory analysis of the data will be conducted as deemed appropriate.

9.3.1. Safety Analyses

9.3.1.1. 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. Adverse events reported to occur prior to enrollment will be distinguished from those reported as new or increased in severity during the study. Each AE will be classified by the most suitable term from the medical regulatory dictionary.

The number of investigational product-related SAEs will be reported.

9.3.1.2. Statistical Evaluation of Safety

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

9.3.2. Pharmacokinetic Analyses

9.3.2.1. Pharmacokinetic Parameter Estimation

Pharmacokinetic parameter estimates will be calculated by standard noncompartmental methods. The primary PK parameters for analysis of selpercatinib will be: $AUC_{0-\infty}$, $AUCt_{last}$, and C_{max}. Other noncompartmental parameters, such as $t_{1/2}$, apparent total body clearance of drug calculated after extravascular administration, and apparent volume of distribution during the terminal phase after extravascular administration, may be reported as appropriate.

9.3.2.2. Pharmacokinetic Statistical Inference

Pharmacokinetic parameters will be evaluated to estimate the effect of food on selpercatinib.

To make a claim of no food effect, the data should be analyzed using an average criterion, with the fasted treatment arm serving as the reference.

Log-transformed C_{max}, $AUC_{0-\infty}$, and AUC_{tlast} parameters for selpercatinib will be evaluated separately. The treatment differences will be back-transformed to present the ratios of geometric means and the corresponding 90% CI. A mixed-effects model with sequence, period (day), and treatment as fixed effects and participant as a random effect will be used.

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.

Pharmacokinetic parameters will be summarized using descriptive statistics.

9.3.3. Pharmacodynamic Analyses

Not applicable for this study.

9.3.4. Pharmacokinetic/Pharmacodynamic Analyses

Not applicable for this study.

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 46 participants will be enrolled to ensure that at least 38 evaluable participants complete the study.

A total of 38 evaluable participants will provide approximately 80% power to have the respective 90% confidence intervals (CIs) for the geometric mean ratios for C_{max} and AUC values between fed and fasted treatments are within the interval of 80% to 125%, assuming a within subject CV of 30% for selpercatinib and that the expected ratio of means is 1.05.

10. Supporting Documentation and Operational Considerations

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

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
    - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
    - Applicable ICH Good Clinical Practice (GCP) Guidelines
    - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (for example, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
    - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
    - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
    - Providing oversight of study conduct for participants under their responsibility and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations
- Investigator sites are compensated for participation in the study as detailed in the clinical trial agreement.

10.1.2. 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 participant and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was entered in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be reconsented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant and is kept on file.

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 study due to safety findings, this decision will be communicated by Lilly to all investigators (for example, by phone and/or email) as soon as possible. It will be a requirement that investigators respond upon receipt to confirm that they understand the communication and have taken the appropriate action prior to further

dosing any participants with study intervention. Any investigator not responding will be followed up by Lilly personnel prior to any further planned dosing. If a dose is planned imminently, Lilly personnel will immediately, and continually, use all efforts to reach investigators until contact is made and instructions verified.

Reports

The sponsor will disclose a summary of study information, including tabular study results, on publicly available websites where required by local law or regulation.

Data

The sponsor does not proactively share data from Phase 1 clinical 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.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (for example, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., contract research organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for the time period outlined in the Clinical Trial Agreement (CTA) unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.
- In addition, 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 a 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 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 10.1.6.

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

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

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

For study termination:

- Discontinuation of further study intervention development

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment (evaluated after a reasonable amount of time) of participants by the investigator
- Total number of participants included earlier than expected.

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

10.1.9. 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

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

10.1.11. Long-Term 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.

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

*Retention periods may differ locally.

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in the table below will be performed by the local laboratory.
- In circumstances where the sponsor approves local laboratory testing in lieu of central laboratory testing (in the table below), the local laboratory must be qualified in accordance with applicable local regulations.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- Investigators must document their review of the laboratory safety results.

Safety Laboratory Tests

Hematology	**Clinical Chemistry**
Hematocrit	Sodium
Hemoglobin	Potassium
Erythrocyte count (RBC)	Bicarbonate
Mean cell volume	Chloride
Mean cell hemoglobin	Calcium
Mean cell hemoglobin concentration	Phosphate
Leukocytes (WBC)	Glucose (random)
Platelets	Cholesterol (total, LDL-C, and HDL-C)
	Total protein
Coagulation[a]	Albumin
Prothrombin time (PTINR)	Total bilirubin
Activated partial thromboplastin time (aPTT)	Alkaline phosphatase (ALP)
	Aspartate aminotransferase (AST)
Differential WBC (absolute counts) of	Alanine aminotransferase (ALT)
Neutrophils	Creatinine
Lymphocytes	Urea
Monocytes	Uric acid
Eosinophils	
Basophils	
Urinalysis	
Specific gravity	
pH	
Protein	
Glucose	
Ketones	
Bilirubin	Hepatitis B surface antigen[a,b]
Urobilinogen	Hepatitis C antibody[a,b,c]
Blood	HIV[a,b]
Nitrite	Pregnancy test (women of childbearing potential only)[f]
Leukocytes	FSH (if applicable)[a,e]
Microscopy[d]	Hepatitis C RNA[c]

Abbreviations: FSH = follicle-stimulating hormone; HIV = human immunodeficiency virus; RBC = red blood cell; WBC = white blood cell.

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

a Performed at screening only.

b Hepatitis B surface antigen test, hepatitis C antibody test, and HIV test may be waived if they have been done 6 months before screening with reports available for review.

c Participants with a positive hepatitis C antibody test result can have a confirmatory hepatitis C RNA test.

d Microscopy to be performed at the local safety laboratory if clinically indicated, per investigator's discretion

e FSH is to be performed for women at screening if needed to confirm postmenopausal status.

f Serum pregnancy tests will be performed at screening and urine pregnancy test at all other time points.

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-JZPA Sampling Summary

Purpose	Blood Volume per Sample (mL)	Maximum Number of Blood Samples	Maximum Total Volume (mL)
Screening tests[a]	23.4	1	23.4
Clinical laboratory tests[a]	8	6	48
Pharmacokinetics - selpercatinib[b]	CCI	CCI	CCI
Blood discard for cannula patency	0.3	34	10.8
Genetic sample	10	1	10
Total			160.2
Total for clinical purposes			170

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

b A maximum of 3 samples may be collected at additional timepoints if warranted, as outlined in Section 8.4.

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

10.3.1. Definition of AE

AE Definition
• 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. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events <u>NOT</u> Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (for example, endoscopy, appendectomy): the condition that leads to the procedure is the AE.

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

10.3.2. Definition of 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 (e.g., 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.

10.3.3. Definition of Product Complaints

Product Complaint

- A product complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness or performance of a study intervention. When the ability to use the study intervention safely is impacted, the following are also product complaints:
  - Deficiencies in labeling information, and
  - Use errors for device or drug-device combination products due to ergonomic design elements of the product.
- Product complaints related to study interventions used in clinical trials are collected 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.

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

AE, SAE, and Product Complaint Recording

- When an AE/SAE/product complaint occurs, it is the responsibility of the investigator to review all documentation (for example, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE/product complaint information in the participant's medical records, in accordance with the investigator's normal

clinical practice. AE/SAE information is reported on the appropriate CRF page and product complaint information is reported on the Product Complaint Form.

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

- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to 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 IB and/or Product Information 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 post-mortem findings including histopathology.

10.3.5. Reporting of SAEs

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 the SAE report.

10.3.6. Regulatory Reporting Requirements

SAE Regulatory Reporting
• Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met. • The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, 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 (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

10.4. Appendix 4: Contraceptive and Barrier Guidance

Definitions:

Woman of Childbearing Potential

Females are considered a woman of childbearing potential if:

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

Any amount of spotting should be considered menarche.

Woman not of Childbearing Potential

Females are considered women not of childbearing potential if:

- they have a congenital anomaly such as Mullerian agenesis,
- they are infertile due to surgical sterilization, or
- they are post-menopausal.

Examples of surgical sterilization include: hysterectomy, bilateral oophorectomy, tubal ligation.

Note: Determination can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

The post-menopausal state is defined as:

1. A woman at any age at least 6 weeks post-surgical bilateral oophorectomy with or without hysterectomy, confirmed by operative note; or
2. A woman at least 40 years of age and up to 55 years of age with an intact uterus, not on hormone therapy*, who has had cessation of menses for at least 12 consecutive months without an alternative medical cause, AND with a follicle-stimulating hormone >40 mIU/mL; or
3. A woman 55 years of age or older not on hormone therapy, who has had at least 12 months of spontaneous amenorrhea; or
4. A woman at least 55 years of age with a diagnosis of menopause prior to starting hormone-replacement therapy.

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

Contraception Guidance:

Males

No male contraception is required except in compliance with specific local government study requirements.

Females

The table below describes contraception guidance for women of childbearing potential who are completely abstinent as their preferred and usual lifestyle, or in a same-sex relationship, as part of their preferred and usual lifestyle:

Must…	**Must not…**

agree to either remain abstinent, or	• use periodic abstinence methods
	  ○ calendar
	  ○ ovulation
	  ○ symptothermal, or
	  ○ post-ovulation
	• declare abstinence just for the duration of a trial, or

stay in a same sex relationship without sexual relationships with males	• use the withdrawal method

The table below describes contraception guidance for women of childbearing potential who are NOT completely abstinent as their preferred and usual lifestyle, or in a same sex relationship, as part of their preferred and usual lifestyle:

Topic	**Explanation**
Pregnancy testing	Negative serum result at screening followed by a negative serum result within 24 hours prior to treatment exposure
	Note: subsequent pregnancy testing is compound specific
Contraception	Must agree to use 2 forms of effective contraception, where at least one form must be highly effective (less than 1% failure rate)

Examples of different forms of contraception:

Methods	**Examples**
Highly effective contraception	• combination oral contraceptive pill and mini-pill • implanted contraceptives • injectable contraceptives • contraceptive patch (only women <198 pounds or 90 kg) • vasectomy (if only sexual partner) • fallopian tube implants (if confirmed by hysterosalpingogram) • combined contraceptive vaginal ring, or • intrauterine devices
Effective contraception	• male or female condoms with spermicide • diaphragms with spermicide or cervical sponges • barrier method with use of a spermicide

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

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 obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of obtaining this consent. 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.

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 advanced or metastatic RET-mutant MTC/advanced or metastatic RET fusion-positive thyroid cancer/metastatic RET fusion-positive NSCLC. They may also be used to develop tests/assays including diagnostic tests related to selpercatinib or advanced or metastatic RET-mutant MTC/advanced or metastatic RET fusion-positive thyroid cancer/metastatic RET fusion-positive NSCLC. 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 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 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

Hepatic Evaluation Testing

See protocol Section 8.2.5.1 for guidance on appropriate test selection.

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

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

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

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

Hepatitis B core IgG antibody	Anti-smooth muscle antibody (ASMA) [a]
HBV DNA [b]	Anti-actin antibody [c]
Hepatis C virus (HCV) testing:	Epstein-Barr virus (EBV) testing:
HCV antibody	EBV antibody
HCV RNA [b]	EBV DNA [b]
Hepatitis D virus (HDV) testing:	Cytomegalovirus (CMV) testing:
HDV antibody	CMV antibody
Hepatitis E virus (HEV) testing:	CMV DNA [b]
HEV IgG antibody	Herpes simplex virus (HSV) testing:
HEV IgM antibody	HSV (Type 1 and 2) antibody
HEV RNA [b]	HSV (Type 1 and 2) DNA [b]
Microbiology [d]	Liver kidney microsomal type 1 (LKM-1) antibody
Culture:	
Blood	
Urine	

[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.

[d] Assayed ONLY by investigator-designated local laboratory; no central testing available.

10.7. Appendix 7: Example of High-Fat Breakfast

A recipe of an example high-fat breakfast that will be provided by the site is provided below. Please note that specifics of this breakfast may change slightly but the overall nutrition of the breakfast will adhere to the guidelines specified in Section 6.1.1.

Ingredients for 4 Servings

100ml	full fat coconut milk (Ayam Brand premium coconut milk)
150ml	chicken stock
50ml	water, for rice
250ml	water, for simmering sambal paste
1 tsp	ginger, ground
1 whole	onion, chopped
50g	garlic
130g	canola oil (Fairprice)
75g	chili raw
25g	chili dried
20g	dried shrimp
15g	sugar white
15g	tamarind
100g	peanuts, roasted
40g	ikan bilis
4	hard boiled eggs
200g	cucumber
190g	white rice (long grain or jasmine)
2 stalks	pandan leaves
1 stalk	lemongrass
0.5tsp	salt
300g	Farmpride tempura chicken nuggets

Instructions

1. Rinse rice
2. Pour 100g coconut milk, 150ml chicken stock, 50ml water, 2 pandan leaves, one lemongrass bashed, 1 tsp minced ginger, 1 Tbsp chopped onions, half tsp salt with rice into rice cooker to cook

3. To make the sambal (follow steps a to g)
    a. blend the remaining onions and garlic with 20ml oil
    b. saute onion and garlic mixture to brown
    c. remove seeds from dried chili, then boil in water till it is soft
    d. soak dried shrimps for 30 minutes
    e. add dried chili, dried shrimps and red chili and blend with 20ml of oil
    f. add chili paste (e) to onion paste (b) to fry
    g. add 250ml of water, tamarind juice, sugar and salt to simmer for 20 minutes on low heat into paste
4. Fry ground nuts with 30ml of oil
5. Fry anchovies with 20ml of oil till crispy
6. Fry chicken Nuggets with 40ml of oil for 3-4min or until golden brown
7. Cut boiled eggs into two halves
8. Cut cucumbers into slices
9. Arrange and serve

Non Vegetarian Breakfast 2

Nutrition Facts

Serving Size: 1 Serving

Amount Per Serving		% Daily Value*
Calories	991.5 kcal	50 %
Total Fat	59.3 g	91 %
Saturated Fat	11.2 g	56 %
Trans Fat	0.1 g	
Cholesterol	262.9 mg	88 %
Sodium	786.7 mg	33 %
Total Carbohydrate	81.9 g	27 %
Dietary Fiber	4.8 g	19 %
Sugars	15.2 g	
Protein	36.9 g	74 %
Vitamin A	17 % • Vitamin C	50 %
Calcium	10 % • Iron	35 %

* Percent Daily Values are based on a 2,000 calorie diet. Your daily values may be higher or lower depending on your calorie needs.

Full Info at cronometer.com </>

Note total fat calories per serve is 533 kcal and total meal calories is 991kcal

10.8. Appendix 8: Abbreviations and Definitions

Term	Definition
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
$AUCt_{last}$	area under the concentration versus time curve from time zero to time t, where t is the last measurable concentration
CIOMS	Council for International Organizations of Medical Sciences
C_{max}	maximum plasma concentration
Companion diagnostic	An in vitro diagnostic device (assay or test) that provides information that is essential for the safe and effective use of a corresponding therapeutic product
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all study-related, good clinical practice (GCP), and applicable regulatory requirements.
CP	clinical pharmacologist
CRF	case report form; a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor for each 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
DMC	data monitoring committee. A data monitoring committee, or data monitoring board (DMB) is a group of independent scientists who are appointed to monitor the safety and scientific integrity of a human research intervention, and to make recommendations to the sponsor regarding the stopping of a study for efficacy, or for harms, or for futility. The composition of the committee is dependent upon the scientific skills and knowledge required for monitoring the particular study.
ECG	electrocardiogram
eCRF	electronic case report form

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
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IMP	Investigational Medicinal Product
INR	international normalized ratio
informed consent	A process by which a participant voluntarily confirms their willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the participant's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
interim analysis	An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created/locked.
investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
ITT	intention to treat: The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a participant (that is, the planned treatment regimen) rather than the actual treatment given. It has the consequence that participant allocated to a treatment group should be followed up, assessed, and analyzed as members of that group irrespective of their compliance to the planned course of treatment.
MTC	medullary thyroid carcinoma
NSCLC	non-small-cell lung cancer
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	corrected QT interval for heart rate by Bazett's formula
QTcF	corrected QT interval for heart rate by Fridericia's formula
RET	ret proto-oncogene
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SoA	Schedule of Activities
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.
TBL	total bilirubin
t_{max}	time to maximum plasma concentration
$t_{1/2}$	half-life associated with the terminal rate constant
ULN	upper limit of normal

Leo Document ID = f62b13ca-0b7b-423c-a6f6-7359a4ff85b3

Approver: PPD

Approval Date & Time: 22-Nov-2021 13:38:16 GMT

Signature meaning: Approved

Approver: PPD

Approval Date & Time: 22-Nov-2021 14:44:17 GMT

Signature meaning: Approved