

An Open-Label, Randomized Study to Evaluate the Relative Bioavailability of Selpercatinib in 3 Formulations for Pediatric Use

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Approval Date: 22-Nov-2021

Title Page

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Protocol Title: An Open-Label, Randomized Study to Evaluate the Relative Bioavailability of Selpercatinib in 3 Formulations for Pediatric Use

Protocol Number: J2G-MC-JZJU

Amendment Number: (b)

Compound: LY3527723

Brief Title: A Relative Bioavailability Study of Selpercatinib Formulations for Pediatric Use

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(s)

IND: 133193

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

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Medical Monitor Name and Contact Information will be provided separately.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	Date
Original Protocol	19-July-2021
Amendment (a)	07-Sep-2021

Amendment [b]

This amendment is considered to be nonsubstantial.

Overall Rationale for the Amendment:

The protocol is amended to correct the timepoints for clinical laboratory assessments in the Schedule of Activities. The following table describes the change made in amendment (b).

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities	<ul style="list-style-type: none"> Physical examination added to Day 21. 	<ul style="list-style-type: none"> Missing assessments added.
1.3 Schedule of Activities	<ul style="list-style-type: none"> Pregnancy test removed from early discontinuation. 	<ul style="list-style-type: none"> Not required.
1.3 Schedule of Activities	<ul style="list-style-type: none"> Added ECG assessments to Day 21. 	<ul style="list-style-type: none"> Missing assessments added.
1.3 Schedule of Activities	<ul style="list-style-type: none"> Added vital signs assessments to Day 21. 	<ul style="list-style-type: none"> Missing assessments added.
1.3 Schedule of Activities	<ul style="list-style-type: none"> Moved time points for collection of clinical laboratory tests from Day 8 to Day 9 (24 hours postdose). Moved time points for collection of clinical laboratory tests from Day 15 to Day 16 (24 hours postdose). Added collection of clinical laboratory tests on Day 21. 	<ul style="list-style-type: none"> To correct the schedule of activities for incorrect and missing clinical laboratory assessment time points.
5.1 Inclusion Criteria	<ul style="list-style-type: none"> Amended the age range for participant inclusion. 	<ul style="list-style-type: none"> Per site request.
10.2 Appendix 2: Clinical Laboratory Tests	<ul style="list-style-type: none"> Added total Cholesterol, HDL-C, and LDL-C as clinical chemistry parameters. 	<ul style="list-style-type: none"> New parameters now required as part of clinical chemistry assessment.
10.2 Appendix 2: Clinical Laboratory Tests	<ul style="list-style-type: none"> Added footnote 'e' to outline timing of pregnancy tests. 	<ul style="list-style-type: none"> For accuracy.

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1. Protocol Summary

1.1. Synopsis

Protocol Title: An Open-Label, Randomized Study to Evaluate the Relative Bioavailability of Selpercatinib in 3 Formulations for Pediatric Use

Brief Title: A Relative Bioavailability Study of Selpercatinib Formulations for Pediatric Use

Rationale:

This is a bioavailability testing the different formulation that has been used in pediatric studies

Objectives, Endpoints, and Estimands:

Objectives	Endpoints
Primary	
<ul style="list-style-type: none"> To evaluate the relative bioavailability of RTU and PFOS suspensions compared to the capsule formulation 	<ul style="list-style-type: none"> C_{max}, $AUC(0-\infty)$, $AUC0-t_{last}$, and t_{max} of selpercatinib
Secondary	<ul style="list-style-type: none"> To evaluate the safety and tolerability of a single dose of 20-mg oral dose of selpercatinib RTU and PFOS suspensions To assess the palatability of selpercatinib RTU and PFOS suspensions

Overall Design:

Study JZJU will be an open-label, Phase 1 randomized, 3-formulation, 3-period, crossover study in adult healthy male and female participants. The ready-to-use (RTU) 20 mg suspension and the powder for oral suspension (PFOS) 20 mg/mL suspension will be compared to the 20 mg capsule formulation

Safety assessments, including AEs, concomitant medications, medical assessments, clinical laboratory tests, vital signs, and ECGs, and blood sampling for PK, will be performed.

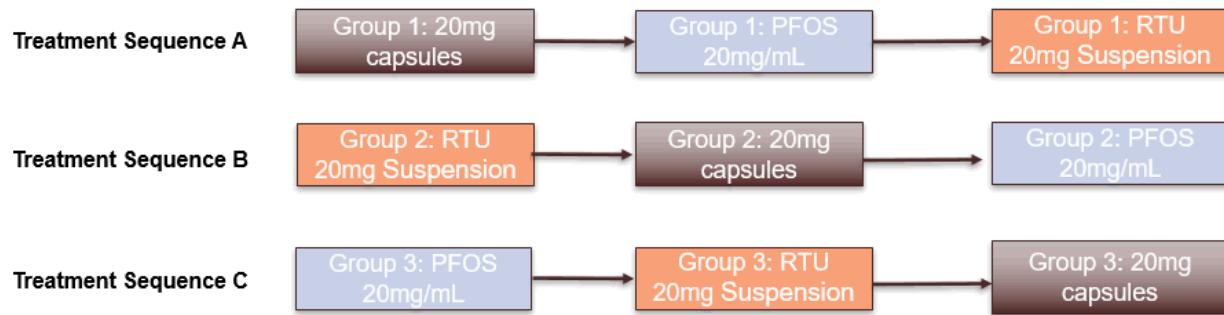
Screening

All participants will be screened within 28 days prior to enrollment.

Treatment and Assessment Period

Participants will be admitted to the CRU on Day -1. On the morning of Day 1, participants will be randomized to 1 of 3 treatment sequences and will receive single doses of 20-mg selpercatinib on each of Days 1, 8, and 15 as either the RTU suspension, the PFOS, or the capsule, and will be dosed according to the randomization sequence following an overnight fast of at least 10 hours.

The treatment sequences to be used are as follows:



Abbreviations: PFOS = powder for oral suspension; RTU = ready to use.

There will be a washout of 7 days between doses of selpercatinib.

Participants will remain resident at the CRU for the full duration of the treatment period (i.e., up to Day 21).

Number of Participants:

Up to approximately 42 participants will be enrolled to ensure that at least approximately 36 participants complete the study.

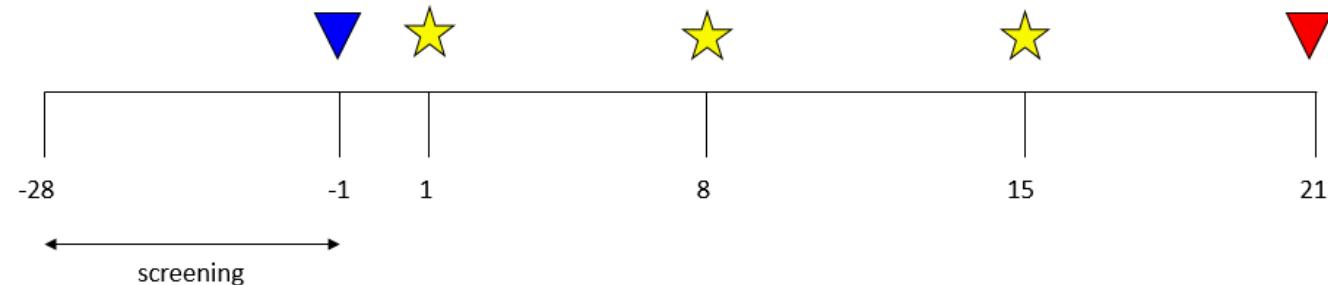
Intervention Groups and Duration:

Participants will participate in 1 treatment.

The study duration for all participants is expected to be up to 59 days.

Data Monitoring Committee: No

1.2. Schema



★ 20 mg selpercatinib as either the RTU suspension, the PFOS, or the capsule, according to the randomization schedule

▼ admission to the CRU

▼ discharge from the CRU / study discharge

Abbreviations: CRU = clinical research unit; PFOS = powder for oral suspension; RTU = ready to use.

1.3. Schedule of Activities (SoA)

Procedure	Screening	Days																					ED	Comments	
		-28 to -2 days prior to Day 1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21		
Informed consent	X																								
Inclusion and exclusion criteria	X																								
Demography	X																								
Participant Admission to CRU		X																							
Participant Discharge from CRU																							X		
Outpatient visit	X																								
Medical history (includes substance usage [and family history of premature cardiovascular disease])		X																							
Past and current medical conditions		X																							
Physical examination	X	X																				X	X	Full physical examination (including height and weight) to be performed at	

Procedure	Screening	Days																					ED	Comments		
		-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21			
	-28 to -2 days prior to Day 1																									
Serum or urine pregnancy test (all females)		X	X																							screening. Symptom-driven physical examinations to be performed at all other timepoints.
HIV, and hepatitis B and C screen		X																								Serum pregnancy test will be performed at screening. Urine pregnancy test will be performed at admission to the CRU.
Urine or breath ethanol test		X	X																							
Urine drug screen		X	X																							
12-lead ECG		X		P, 2h						P, 2h						P, 2h					X	X			Single ECGs are required.	
Vital signs (supine)		X	X	P, 1, 2h	24 h			X		P, 1, 2h	24 h			X		P, 1, 2h	24 h			X	X	X			Time points may be added, if warranted and agreed upon between	

Procedure	Screening	Days																					ED	Comments	
		1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21		
	-28 to -2 days prior to Day 1																								Lilly and the investigator. Assessments on Days 5 12, and 19 should be performed in the morning at a time relative to predose on Days 1, 8 and 15, respectively.
Clinical laboratory tests (include liver chemistries)	X	X		24 h					X	24 h					X		24 h					X	X	See Appendix 2 (Section 10.2), Clinical Laboratory Tests, for details.	
Genetic sample			X																						

CCI

	Screening	Days																					ED	Comments	
Procedure	-28 to -2 days prior to Day 1	1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21		
		CCI																							
Randomization			X																						
Selpercatinib administration			X							X								X							
Taste Assessment Questionnaire				X							X							X							To be performed for the RTU suspension and PFOS formulations only immediately after dosing.
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; HIV = human immunodeficiency virus; P = predose; PFOS = powder for oral suspension; PK = pharmacokinetic; RTU = ready to use.

2. Introduction

Selpercatinib (LY3527723) has been developed by Loxo Oncology, Inc and acquired by Eli Lilly and Company (Lilly), and has been approved by the Food and Drug Administration for the treatment of advanced or metastatic RET-mutant MTC; advanced or metastatic RET fusion-positive thyroid cancer, in adults and children ≥ 12 years; and for the treatment of metastatic RET fusion-positive non-small cell lung carcinoma (NSCLC) in adults. Full details of the preclinical and clinical safety and tolerability data are contained in the investigator's brochure (IB).

2.1. Study Rationale

This is a relative bioavailability study testing the different formulations that has been used in pediatric studies.

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.

Selpercatinib doses have been evaluated in healthy participants and patients with advanced or metastatic RET-mutant MTC, advanced or metastatic RET fusion-positive thyroid cancer, other RET fusion-positive solid tumors, 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. Multiple oral doses of 160 mg/day selpercatinib were administered orally twice daily for 10 days in healthy volunteers. Pediatric dose was selected to be 92 mg/m^2 , (maximum 160 mg BID).

The pharmacokinetics of selpercatinib is characterized by good oral bioavailability, with a t_{max} of approximately 2 hours (range 0 to 8.1 hours). CYP3A4 mediated metabolism constitutes the major route of elimination, and the $t_{\frac{1}{2}}$ is approximately 32 hours in healthy volunteers. The $V_{\text{ss/F}}$ and CL/F of selpercatinib increased with increasing body weight (27 kg to 177 kg). No clinically significant differences in the PK of selpercatinib were observed based on age (15 years to 90 years), or sex. As the PK of selpercatinib have been demonstrated to be linear in the dose range of 20 to 160 mg in adult cancer patients, results from study JZJU can be expected to be applicable across the therapeutic dose range.

More detailed information about the pharmacokinetics (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 healthy 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 20 mg. The safety profile of selpercatinib is very well tolerated in healthy volunteers, with the low rates of study drug discontinuation due to adverse events (AEs).

As outlined in the IB, the most common toxicities associated with selpercatinib in patients are monitorable and reversible and include dry mouth, diarrhea, hypertension, fatigue, constipation, AST/ALT elevation, headache, nausea, edema peripheral, abdominal pain, rash, electrocardiogram (ECG) QT prolonged, cough, vomiting, dyspnea and increased blood creatinine. Events of special interest include hypersensitivity, liver-function test abnormalities, thrombocytopenia, and hypertension. None of these events of special interest have been observed to date in healthy participants.

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

3. Objectives and Endpoints

Objectives	Endpoints
Primary	
<ul style="list-style-type: none"> To evaluate the relative bioavailability of RTU and PFOS suspensions compared to the capsule formulation 	<ul style="list-style-type: none"> C_{max}, $AUC(0-\infty)$, $AUC0-t_{last}$, and t_{max} of selpercatinib
Secondary	<ul style="list-style-type: none"> To evaluate the safety and tolerability of a single 20-mg oral dose of selpercatinib RTU and PFOS suspensions To assess the palatability of selpercatinib RTU and PFOS suspensions
	<ul style="list-style-type: none"> Summary of the number, severity, and type of treatment-emergent AEs and serious adverse events Responses to palatability questionnaire (RTU suspension only)

Abbreviations: AE = adverse event; $AUC(0-\infty)$ = area under the concentration versus time curve from time zero to infinity; $AUC0-t_{last}$ = area under the concentration versus time curve from time zero to time t , where t is the last time point with a measurable concentration; C_{max} = maximum observed drug concentration; PFOS = powder for oral suspension; RTU = ready to use; t_{max} = time to maximum observed drug concentration.

4. Study Design

4.1. Overall Design

Study JZJU will be an open-label, Phase 1 randomized, 3-formulation, 3-period, crossover study in adult healthy male and female participants. The ready-to-use (RTU) 20-mg suspension and the powder for oral suspension (PFOS) 20 mg/mL formulation will be compared to the 20 mg capsule formulation.

The schematic in Section 1.2 illustrates the study design.

Safety assessments, including AEs, concomitant medications, medical assessments, clinical laboratory tests, vital signs, and ECGs, and blood sampling for PK, will be performed according to the SoA (Section 1.3).

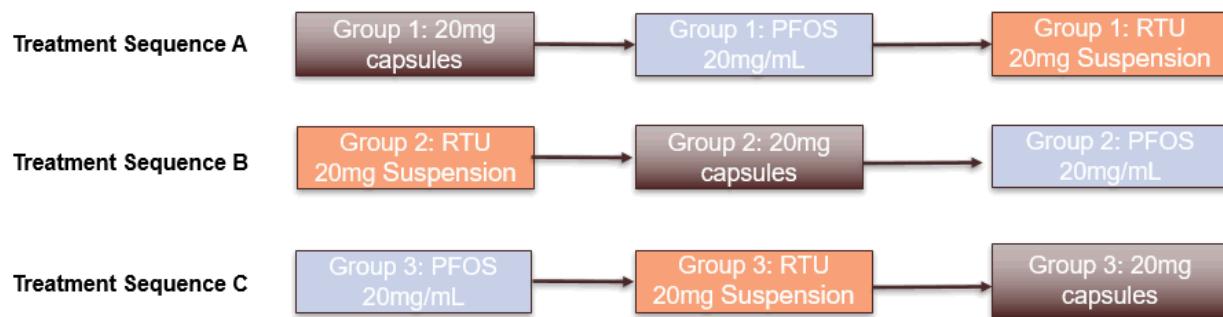
4.1.1. Screening

All participants will be screened within 28 days prior to enrollment.

4.1.2. Treatment and Assessment Period

Participants will be admitted to the clinical research unit (CRU) on Day -1. On the morning of Day 1, participants will be randomized to 1 of 3 treatment sequences and will receive single doses of 20 mg selpercatinib on each of Days 1, 8, and 15 as either the RTU suspension, the PFOS, or the capsule, and will be dosed according to the randomization sequence following an overnight fast of at least 10 hours.

The treatment sequences to be used are as follows:



Abbreviations: PFOS = powder for oral suspension; RTU = ready to use.

There will be a washout of 7 days between doses of selpercatinib.

Participants will remain resident at the CRU for the full duration of the treatment period (i.e., up to Day 21).

4.2. Scientific Rationale for Study Design

In order to allow each participant to act as his/her own control for safety and PK comparisons, a 3-period crossover design has been selected. This study will also be open label as the study primary endpoint PK measures are objective rather than subjective.

Conducting the study in healthy adult 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.

The doses, participant population, study duration, and sample collection timing are considered adequate to achieve the study objectives.

4.3. Justification for Dose

Dose being used is representative of the typical dose size to be used in pediatric studies. As the PK of selpercatinib have been demonstrated to be linear in the dose range of CCI in adult cancer patients, results from study JZJU can be expected to be applicable across the therapeutic dose range.

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all required periods of the study including the last visit or the last scheduled procedure shown in the SoA.

The end of the study is defined as the date of the last visit of 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 18 to 65 years of age, inclusive, at the time of signing the informed consent form (ICF).

Type of Participant and Disease Characteristics

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 18.0 to 35.0 kg/m² (inclusive).

Sex and Contraceptive/Barrier Requirements

6. Male or female participants - 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:
 - Are not required to adhere to contraceptive requirements.

b. Female participants:

- Female participants of childbearing potential (see Appendix 4 [Section 10.4]) who are abstinent (if this is complete abstinence, as their preferred and usual lifestyle) or in a same-sex relationship (as part of their preferred and usual lifestyle) must agree to either remain abstinent or stay in a same-sex relationship without sexual relationships with males.
Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence just for the duration of a study, and withdrawal, are not acceptable methods of contraception.
- Female participants of childbearing potential, who are not abstinent as described above, must agree to use a highly effective method of contraception (that is, one with less than 1% failure rate) such as combination oral contraceptives, implanted/injected contraceptives, intrauterine devices, or sterile partner until 30 days after the last dose of study medication.
- Female participants not of childbearing potential are not required to use contraception. This includes females who are:
 - Infertile due to surgical sterilization (hysterectomy, bilateral oophorectomy, bilateral salpingectomy, bilateral tubal occlusion, or bilateral tubal ligation), or congenital anomaly (for example, Müllerian agenesis)
 - Postmenopausal as defined in Appendix 4 (Section 10.4).

Informed Consent

7. Capable of giving signed informed consent as described in Appendix 1 (Section 10.1), which includes compliance with the requirements and restrictions listed in the 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-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. Clinically significant abnormalities on ECG as determined by the investigator or prolongation of the corrected QT interval using or Fridericia's formula (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, uncomplicated hernia, splenectomy, and cholecystectomy are considered as acceptable.
10. Have a creatinine clearance <60 mL/min, as calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (Levey et al, 2009).
$$\text{eGFR} = 141 \times \min(\text{Scr}/\text{K}, 1)^\alpha \times \max(\text{Scr}/\text{K}, 1)^{-1.209} \times 0.993^{\text{age}}$$
$$\times 1.018 \text{ (if female)}$$
$$\times 1.159 \text{ (if black)}$$
11. 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.
12. Have a history or presence of neuropsychiatric disease (e.g., bipolar disorder, schizophrenia, depression) considered as clinically significant by the investigator.
13. Regularly use known drugs of abuse or show positive findings on drug screening.
14. Show evidence of human immunodeficiency virus infection and/or positive human immunodeficiency virus antibodies.
15. Presence of hepatitis B surface antigen at screening or within 3 months prior to first dose of study intervention.
16. Positive hepatitis C antibody test result at screening or within 3 months prior to first dose of study intervention.
NOTE: Participants with positive hepatitis C antibody due to prior resolved disease can be enrolled if a confirmatory negative hepatitis C RNA test is obtained.
17. Positive hepatitis C RNA test result at screening or within 3 months prior to first dose of study intervention.
NOTE: Test is optional and participants with negative hepatitis C antibody test are not required to also undergo hepatitis C RNA testing.
18. Have donated blood of more than 500 mL within the previous 3 months of study screening.
19. Have any medical conditions, medical history, or are taking any medications that are contraindicated in the selpercatinib label.

■

20. Have participated, within the last 30 days of admission, in a clinical study involving an investigational product. If the previous investigational product has a long half-life, 5 half-lives or 30 days (whichever is longer) should have passed.
21. Have previously completed or withdrawn from this study or any other study investigating selpercatinib, and have previously received the investigational product.

22. Use of H₂ blockers, proton-pump inhibitors, and other antacids within 7 days of screening.
23. 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 (≤ 2 g/24 hours), hormonal contraception, or hormone-replacement therapy).
- P**
24. Are currently enrolled in any other clinical study involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study
- D**
25. 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)
26. Are unwilling to stop alcohol consumption 48 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
27. Are smokers of more than 10 cigarettes or e-cigarettes, or 3 cigars or 3 pipes, per day and are unable to refrain from smoking while resident at the CRU
28. Consume excessive amounts of coffee, tea, cola, or other caffeinated beverages per day, or are unwilling to stop caffeine consumption 48 hours prior to admission and while resident at the CRU. Excessive amount is defined as greater than 6 servings (1 serving is approximately equivalent to 120 mg of caffeine).
29. Are unable to consume a standard meal.
30. 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
31. Inability to comply with the dietary regimen of the CRU
32. Are Lilly employees or are an employee of any third party involved in the study who require exclusion of their employees
33. 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
34. In the opinion of the investigator or sponsor, are unsuitable for inclusion in the study

5 **█**

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

5.3.1. Meals and Dietary Restrictions

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.

Selpercatinib will be dosed in the fasted state on Days 1, 8, and 15. On these dosing occasions, the participants will be fasted overnight (at least 10 hours) prior to dosing and refrain from consuming water from 1 hour predose until 2 hours postdose, excluding the amount of water consumed at dosing. Food is allowed from 4 hours postdose. At all other times during the study, participants may consume water ad libitum.

5.3.2. Caffeine, Alcohol, and Tobacco

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

Participants will abstain from alcohol for 48 prior to admission until after discharge from the study.

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 clinical unit.

5.3.3. Activity

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

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently assigned to study intervention.

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(s) Administered

Table JZJU.1. Study Interventions Administered

Arm Name	Capsule	Ready to use	PFOS
Study Intervention	Selpercatinib	Selpercatinib	Selpercatinib
Dosage Formulation	Capsule	Suspension	Suspension
Unit dose strengths/Dosage Levels	1 × 20-mg capsule	20 mg/mL	20 mg/mL
Route of Administration	Oral	Oral	Oral
Dosing Instructions	1 capsule taken on Day 1, 8, or 15, according to the randomization schedule	1 mL taken on Day 1, 8, or 15, according to the randomization schedule	1 mL taken on Day 1, 8, or 15, according to the randomization schedule

Abbreviations: PFOS = powder for oral suspension.

6.1.1. Administration Details

A single oral dose of selpercatinib 20 mg will be administered in the morning of Days 1, 8, and 15. Capsules and suspension of selpercatinib will be administered with approximately 240mL of room-temperature water. All doses will be administered while in a sitting position. Participants will not be allowed to lie supine for 2 hours after dosing, unless clinically indicated or for study procedures.

Selpercatinib capsules should be swallowed whole. Participants should not break, empty, or chew the capsules.

Further instructions will be provided.

On dosing days, participants will adhere to meal restrictions as outlined in Section 5.3.1.

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

Note: in some cases, sites may destroy the material if the evaluator has verified and documented that the site has appropriate facilities and written procedures to dispose of clinical materials.

Samples of the specific batches of selpercatinib used in the study will be retained; details will be provided separately.

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.

Participants will be assigned a unique number (randomization number) on Day 1. The randomization number encodes the participant's assignment to be dosed with either the capsule, RTU suspension, or PFOS on Days 1, 8, and 15, according to the randomization schedule generated prior to the study by the Statistics Department at Covance.

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 electronic case report form (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.

When the individual dose for a participant is prepared from a bulk supply, the preparation of the dose will be confirmed by a second member of the study site staff.

6.5. Dose Modification

Dose modification will not be permitted in this study.

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

Selpercatinib will not be made available to participants after completion of the study.

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:

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

Decisions regarding dose interruptions will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

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:

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

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Participants must abstain from taking prescription or nonprescription drugs (including vitamins and dietary or herbal supplements) within 14 days before the start of study intervention until discharge from the study.

Acetaminophen, at doses of ≤ 2 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 clinical pharmacologist (CP)/clinical research physician (CRP), or designee.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

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

Discontinuation of the study as a whole is described in Appendix 1 (Section 10.1).

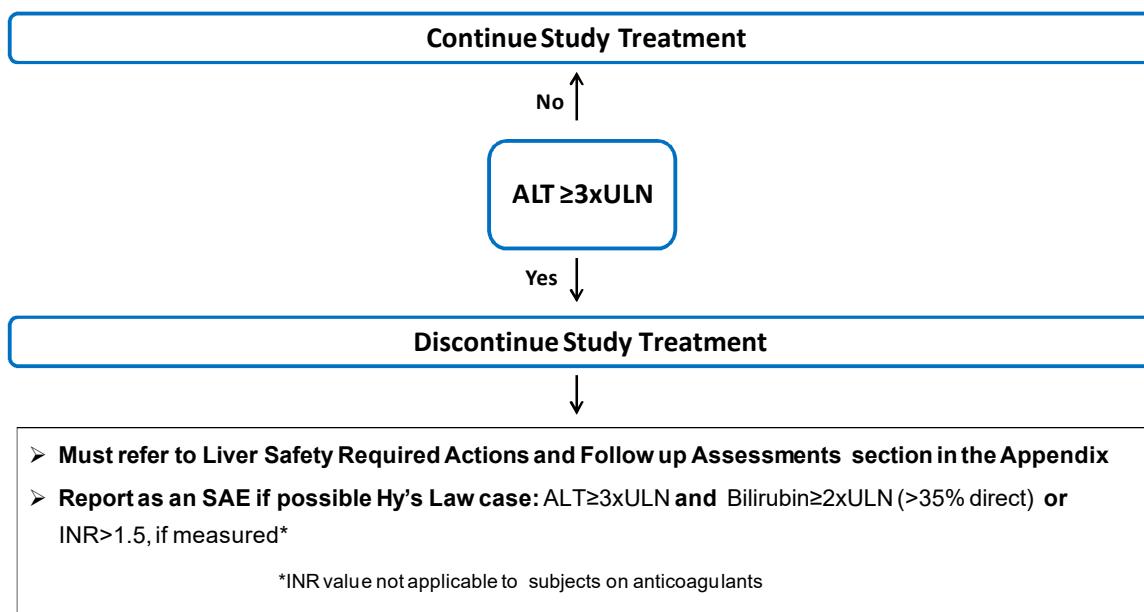
7.1. Discontinuation of Study Intervention

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 discharge from the study, 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



Abbreviations: ALT = alanine transaminase; INR = international normalized ratio; SAE = serious adverse event; ULN = upper limit of normal.

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 will be withdrawn from the study.

- QTc, QTcB, or QTcF >500 msec
- Change from baseline: 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 discharge from the study, 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 his/her own request
- at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons
- if the participant becomes pregnant during the study
- if enrolled in any other clinical study involving an investigational product or enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study
- if the participant, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication, discontinuation from the study occurs prior to introduction of the new agent.

Discontinuation is expected to be uncommon.

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

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

7.3. Lost to Follow-up

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

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

8. Study Assessments and Procedures

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

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

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

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

8.1. Efficacy Assessments

Not applicable to this study.

8.2. Safety Assessments

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

8.2.1. Physical Examinations

Physical examinations should be conducted according to the SoA (Section 1.3).

A full physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems. Height and weight will also be measured and recorded.

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

8.2.2. Vital Signs

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

Blood pressure and pulse rate should be measured 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.

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*

For each participant, single 12-lead ECGs will be obtained as outlined in the SoA (see Section 1.3). Refer to Section 7 for QTc withdrawal criteria and any additional QTc readings that may be necessary.

Electrocardiograms must be recorded before collecting any blood samples. Participants must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection. Electrocardiograms may be obtained at additional times, when deemed clinically necessary. All ECGs recorded should be stored at the investigational site.

Electrocardiograms 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 baseline) after enrollment, the investigator will determine if the participant can continue in the study. The investigator, or qualified designee, is responsible for determining if any change in participant management is needed and must document his/her review of the ECG printed at the time of collection. Any new clinically relevant finding should be reported as an AE.

8.2.4. *Clinical Safety Laboratory Tests*

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

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents.

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

- If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the sponsor notified.
- All protocol-required laboratory assessments, as defined in Appendix 2 (Section 10.2), must be conducted in accordance with the laboratory manual and the SoA.

If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., SAE or AE), then the results must be recorded in the eCRF.

8.2.5. *Pregnancy Testing*

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

8.2.6. Safety Monitoring

The Lilly CP or CRP/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.

8.2.6.1. Hepatic Safety

Close hepatic monitoring

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

If a participant with baseline results of ...	develops the following elevations:
ALT or AST $<1.5 \times$ upper limit of normal (ULN)	ALT or AST $\geq 3 \times$ ULN
ALP $<1.5 \times$ ULN	ALP $\geq 2 \times$ ULN
TBL $<1.5 \times$ ULN	TBL $\geq 2 \times$ ULN (except for patients with Gilbert's syndrome)
ALT or AST $\geq 1.5 \times$ ULN	ALT or AST $\geq 2 \times$ baseline
ALP $\geq 1.5 \times$ ULN	ALP $\geq 2 \times$ baseline
TBL $\geq 1.5 \times$ ULN	TBL $\geq 2 \times$ 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 physical examination and a thorough medical history, including symptoms, recent illnesses (for example, heart failure, systemic infection, hypotension, or seizures), recent travel, history of concomitant medications (including over-the-counter), herbal and dietary supplements, and history of alcohol drinking and other substance abuse.

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

Comprehensive hepatic evaluation

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

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

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

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

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

Additional hepatic data collection (hepatic safety eCRF) in study participants who have abnormal liver tests during the study:

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

1. Elevation of serum ALT to $\geq 5 \times$ ULN on 2 or more consecutive blood tests (if baseline ALT $<1.5 \times$ ULN)
 - In participants with baseline ALT $\geq 1.5 \times$ ULN, the threshold is ALT $\geq 3 \times$ baseline on 2 or more consecutive tests
2. Elevated TBL to $\geq 2 \times$ ULN (if baseline TBL $<1.5 \times$ ULN) (except for cases of known Gilbert's syndrome)
 - In participants with baseline TBL $\geq 1.5 \times$ ULN, the threshold should be TBL $\geq 2 \times$ baseline
3. Elevation of serum ALP to $\geq 2 \times$ ULN on 2 or more consecutive blood tests (if baseline ALP $<1.5 \times$ ULN)

- In participants with baseline ALP $\geq 1.5 \times$ ULN, the threshold is ALP $\geq 2 \times$ baseline on 2 or more consecutive blood tests
- 4. Hepatic event considered to be an 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

Product Complaints are covered in Section [8.3.3](#).

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

- AEs
- SAEs
- Product complaints (PCs)

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

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

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

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 eCRF	N/A
Serious Adverse Event					

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-up Method of Reporting
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)	SAE paper form	SAE 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
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

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

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 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 learning of the partner's pregnancy. 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 poststudy 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 discontinue study intervention. If the participant is discontinued from the study, follow the standard discontinuation process and continue directly to the follow-up phase. The follow-up on the pregnancy outcome should continue independent of intervention or study discontinuation.

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

- The sponsor and the relevant institutional review board (IRB)/independent ethics committee (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 her offspring.

8.3.3. Product Complaints

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.

The sponsor collects PCs on investigational products and drug delivery systems used in clinical studies in order to ensure the safety of study participants, monitor quality, and to facilitate process and product improvements.

Participants will be instructed to contact the investigator as soon as possible if he or she has a complaint or problem with the investigational product so that the situation can be assessed.

NOTE: AEs/SAEs that are associated with a product complaint will also follow the processes outlined in Section 8.3.1 and Appendix 3 (Section 10.3) of the protocol.

8.4. Pharmacokinetics

- Venous blood 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 OR saliva 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) 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

This section is not applicable for this study.

8.10. Product Acceptability and Palatability Assessments

The participant will be asked to provide responses to questions designed to assess the acceptability and palatability of the RTU suspension. The questionnaire will assess the participant's experience relating to the taste, smell, and after taste in the oral cavity.

The questionnaire will be completed by the participant immediately after administration of the RTU suspension and PFOS formulations.

9. Statistical Considerations

9.1. Statistical Hypotheses

The primary objective will be evaluated to assess the relative bioavailability of the RTU suspension and drug-in-bottle formulations compared to the commercial formulation (capsule).

9.2. Analyses Sets

The following populations are defined:

Population	Description
Entered	All participants who sign the ICF.
Safety	All enrolled participants who take at least 1 dose of selpercatinib, whether or not they completed all protocol requirements.
Pharmacokinetic Analysis	All participants who received at least 1 dose of selpercatinib 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.

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.

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

Safety analyses will be conducted for all enrolled participants who received at least 1 dose of selpercatinib, whether or not they completed all protocol requirements.

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

9.3.1. Safety Analyses

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.

9.3.1.1. Statistical Evaluation of Safety

Safety parameters that will be assessed include safety laboratory parameters, vital signs, and ECG parameters. 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: maximum observed drug concentration (C_{max}), area under the concentration versus time curve from time zero to infinity ($AUC[0-\infty]$), area under the concentration versus time curve from time zero to time t , where t is the last time point with a measurable concentration ($AUC0-t_{last}$), and time to C_{max} (t_{max}).

Other noncompartmental parameters, such as terminal half-life ($t_{1/2}$), 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 relative bioavailability. For the primary analysis, log-transformed C_{max} , $AUC(0-\infty)$, and $AUC0-t_{last}$ will be evaluated in a linear mixed-effect model with fixed effects for formulation, period, and sequence, and a random effect for subject. The treatment differences will be back-transformed to present the ratios of geometric means and the corresponding confidence intervals (CIs).

For secondary analysis, 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

Up to approximately 42 participants will be enrolled to ensure that at least approximately 36 participants complete the study. The sample size for this study is justified based on a precision for the ratio of geometric means and it is represented by the half-width of the 90% CI of the point estimate on the logarithmic scale. Based on an intra-subject variability of 70% (LOXO-RET-19075), with a probability of 90%, a 90% CI for the ratio of the geometric means for C_{max} and AUC will be obtained with a precision about 0.288 in the log scale, which corresponds to approximately 0.334 in the natural scale.

10. Supporting Documentation and Operational Considerations

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

10.1.1. Regulatory and Ethical Considerations

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

10.1.2. Informed Consent Process

- The investigator or his/her 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.

10.1.3. Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records, datasets or tissue samples that are transferred to the sponsor will contain the identifier only; participant names or any information that would make the participant identifiable will not be transferred.
- The participant must be informed that his/her 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 his/her data to be used as described in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The sponsor has processes in place to ensure data protection, information security and data integrity. These processes include appropriate contingency plan(s) for appropriate and timely response in the event of a data security breach.

10.1.4. Dissemination of Clinical Study Data**Communication of Suspended or Terminated Dosing**

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

imminently, Lilly personnel will immediately, and continually, use all efforts to reach investigators until contact is made and instructions verified.

Reports

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

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.

10.1.5. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRFs unless transmitted to the sponsor or designee electronically (for example, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Quality tolerance limits (QTLs) will be predefined to identify systematic issues that can impact participant safety and/or reliability of study results. These pre-defined parameters will be monitored during the study and important excursions from the QTLs and remedial actions taken will be summarized in the clinical study report.
- Monitoring details describing strategy (for example, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques, are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., contract research organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for the time period outlined in the Clinical Trial Agreement unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.
- In addition, the sponsor or its representatives will periodically check a sample of the participant data recorded against source documents at the study site. The study may be audited by the sponsor or its representatives, 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 eCRF data. The investigator maintains a separate source for the data entered by the investigator or designee into the sponsor-provided EDC system. The investigator is responsible for the identification of any data to be considered source and for the confirmation that data reported are accurate and complete by signing the eCRF.

Data collected via a 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 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.

10.1.6. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in Section 10.1.4.

10.1.7. Study and Site Start and Closure

First Act of Recruitment

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

Study or Site Termination

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

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

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

For study termination:

- Discontinuation of further study intervention development.

For site termination:

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

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

10.1.8. Publication Policy

In accordance with the sponsor's publication policy, the results of this study will be submitted for publication by a peer-reviewed journal if the results are deemed to be of significant medical importance.

10.2. Appendix 2: Clinical Laboratory Tests

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

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

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

Investigators must document their review of the laboratory safety results.

Safety Laboratory Tests

Hematology	Clinical Chemistry
Hematocrit	Sodium
Hemoglobin	Potassium
Erythrocyte count (RBC)	Bicarbonate (total CO ₂)
Mean cell volume	Chloride
Mean cell hemoglobin	Calcium
Mean cell hemoglobin concentration	Phosphorus
Leukocytes (WBC)	Glucose (random)
Platelets	Creatine kinase
Differential WBC (absolute counts) of	
Neutrophils	Blood urea nitrogen (BUN)
Lymphocytes	Uric acid
Monocytes	Total Cholesterol, HDL-C, LDL-C
Eosinophils	Total protein
Basophils	Albumin
Urinalysis^a	
Specific gravity	Total bilirubin
pH	Alkaline phosphatase (ALP)
Protein	Aspartate aminotransferase (AST)
Glucose	Alanine aminotransferase (ALT)
Ketones	Creatinine
Bilirubin	Ethanol testing ^b
Urobilinogen	Urine drug screen ^b
Blood	Hepatitis B surface antigen ^c
Nitrite	Hepatitis C antibody ^{c, d}
Leukocyte esterase	HIV ^c
	Pregnancy teste
	FSH (if applicable) ^c

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

^a Performed by dipstick. Reflex microscopy to be performed if microscopy is abnormal.

^b Urine drug screen and ethanol (urine or breath) level performed at screening, and may be repeated prior to admission to the Clinical Research Unit.

^c Performed at screening only.

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

^e Screening and Day -1 only.

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-JZJU Sampling Summary

Purpose	Blood Volume per Sample (mL)	Number of Blood Samples	Total Volume (mL)
Screening tests ^a	45	1	45
Clinical laboratory tests ^a	12	7	84
CC1 [REDACTED]	[REDACTED]	[REDACTED]	CC1 [REDACTED]
Blood discard for cannula patency	1	1	1
Genetic sample	10	1	10
Total			260
Total for clinical purposes			260

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

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

- An AE is any untoward medical occurrence in a participant administered a pharmaceutical product and which does not necessarily have a causal relationship with the study intervention. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Events Meeting the AE Definition

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

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- The disease/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:

d. Results in death

e. 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.

f. 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.

g. 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.

h. Is a congenital anomaly/birth defect

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

i. 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 eCRF page and product complaint information is reported on the Product Complaint Form.

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

- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the sponsor or designee in lieu of completion of the eCRF page for AE/SAE and the Product Complaint Form for product complaints.
- There may be instances when copies of medical records for certain cases are requested by the sponsor or designee. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the sponsor or designee.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will 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 an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

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

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the IB in his/her assessment.

- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor or designee. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor or designee.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor or designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor or designee with a copy of any post-mortem findings including histopathology.

10.3.5. Reporting of SAEs

SAE Reporting via Paper Form

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

10.3.6. Regulatory Reporting Requirements

SAE Regulatory Reporting

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

- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Definitions

Woman of Childbearing Potential

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered women of childbearing potential

1. Premenarchal
2. Premenopausal female with 1 of the following:
 - Documented hysterectomy
 - Documented bilateral salpingectomy
 - Documented bilateral oophorectomy
 - Documented bilateral tubal ligation
 - Bilateral tubal occlusion

For individuals with permanent infertility due to an alternate medical cause other than the above (e.g., Müllerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

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

3. Postmenopausal female is defined as women with:
 - 12 months of amenorrhea for women ≥ 55 , with no need for follicle-stimulating hormone
 - 12 months of amenorrhea for women > 40 to ≤ 54 years old with follicle-stimulating hormone ≥ 40 mIU/mL and no other medical condition such as anorexia nervosa and not taking medications during the amenorrhea (e.g., oral contraceptives, hormones, gonadotropin-releasing hormone, anti-estrogens, selective estrogen-receptor modulators, or chemotherapy that induced amenorrhea)

10.4.2. Contraception Guidance

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

Male participants:

- are not required to adhere to contraceptive requirements

Female participants:

- Female participants of childbearing potential who are abstinent (if this is complete abstinence, as their preferred and usual lifestyle) or in a same-sex relationship (as part of their preferred and usual lifestyle) must agree to either remain abstinent or stay in a same-sex relationship without sexual relationships with males. Periodic abstinence (e.g.,

calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence just for the duration of a study, and withdrawal are not acceptable methods of contraception.

- Female participants of childbearing potential, who are not abstinent as described above, must agree to use a highly effective method of contraception (that is, one with less than 1% failure rate) such as combination or oral contraceptives, implanted/injected contraceptives, intrauterine devices, or sterile partner until 30 days after the last dose of study medication.
 - Female participants not of childbearing potential are not required to use contraception. This includes females who are:
 - Infertile due to surgical sterilization (hysterectomy, bilateral oophorectomy, bilateral salpingectomy, bilateral tubal occlusion or tubal ligation) or congenital anomaly (for example, Müllerian agenesis)
 - Postmenopausal, as defined above.

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 learning of the partner's pregnancy. 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 including fetal status (presence or absence of anomalies) and 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, including fetal status (presence or absence of anomalies) or indication for the procedure.

- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion (occurring at <20 weeks gestational age) or still birth (occurring at >20 weeks gestational age) is always considered to be an SAE and will be reported as such.
- Any poststudy pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.3.2. 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 discontinue study intervention. If the participant is discontinued from the study intervention, follow the standard discontinuation process and continue directly to the follow-up phase.

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/saliva 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 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 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 or indication continues but no longer than 15 years or other period as per local requirements.

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

Hepatic Evaluation Testing – Refer to protocol Hepatic Safety Section 8.2.6.1 for guidance on appropriate test selection.

- For testing selected, analysis is required to be completed by the Lilly-designated central laboratory except for Microbiology.
- Local testing may be performed in addition to central testing when required 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
Coagulation	Copper
	Ethyl Alcohol (EtOH)
Prothrombin Time, International Normalized Ratio (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)
Hepatitis B Virus (HBV) Testing:	Urine Chemistry
Hepatitis B surface antigen (HBsAg)	Drug Screen
Hepatitis B surface antibody (Anti-HBs)	Ethyl glucuronide (EtG)
Hepatitis B core total antibody (Anti-HBc)	Other Serology
Hepatitis B core IgM antibody	Anti-nuclear antibody (ANA)
Hepatitis B core IgG antibody	Anti-smooth muscle antibody (ASMA) ^a

HBV DNA ^d	Anti-actin antibody ^b
Hepatitis C Virus (HCV) Testing:	Epstein-Barr Virus (EBV) Testing:
HCV antibody	EBV antibody
HCV RNA ^d	EBV DNA ^d
Hepatitis D Virus (HDV) Testing:	Cytomegalovirus (CMV) Testing:
HDV antibody	CMV antibody
Hepatitis E Virus (HEV) Testing:	CMV DNA ^d
HEV IgG antibody	Herpes Simplex Virus (HSV) Testing:
HEV IgM antibody	HSV (Type 1 and 2) antibody
HEV RNA ^d	HSV (Type 1 and 2) DNA ^d
Microbiology ^c	Liver Kidney Microsomal Type 1 (LKM-1) Antibody
Culture:	
Blood	
Urine	

^a This is not required if anti-actin antibody is tested.

^b This is not required if ASMA is tested.

^c Assayed by investigator-designated local laboratory ONLY; no Central Testing available.

^d Reflex/confirmation dependent on regulatory requirements and/or testing availability.

Evaluation of participants with treatment-emergent abnormal hepatic biochemical tests during a clinical trial *

Test/Procedure:	Rationale	Action
Close Hepatic Monitoring		
Clinical Chemistry: Total bilirubin Direct bilirubin Alkaline phosphatase (ALP) Alanine aminotransferase (ALT) Aspartate aminotransferase (AST) ^b Gamma-glutamyl transferase (GGT) Creatine kinase (CK)	All: Routine follow-up CK: Muscle injury/rhabdomyolysis	Utilize a Hepatic Monitoring central lab collection kit and select Clinical Chemistry
Hematology Hemoglobin Hematocrit Erythrocytes (RBCs – Red Blood Cells) Leukocytes (WBCs – White Blood Cells) Differential: Neutrophils, segmented	Infection	Utilize a Hepatic Monitoring central lab collection kit and select Hematology

Lymphocytes Monocytes Basophils Eosinophils Platelets Cell Morphology (RBCs and WBCs)		
Medical history: ^{a, h} Symptoms Co-existing medical conditions Concomitant medications Dietary and nutritional supplements Exercise (excessive) Muscle Injury Alcohol consumption Illicit substances	Used to evaluate/rule out: Systemic infection or sepsis Ischemic or congestive hepatic injury Gallstone disease Alcoholic liver disease Muscle injury/rhabdomyolysis Acetaminophen toxicity Drug-Induced Liver Injury (DILI) due to another drug, herbal or dietary substances	If findings are clinically significant, report as an adverse event.
Hepatitis A Virus (HAV) Testing: HAV Total Antibody HAV IgM Antibody	Used to evaluate/rule out: Acute HAV infection	Utilize a Hepatic Monitoring central lab collection kit and select Hepatitis A
Hepatitis B Virus (HBV) Testing: Hepatitis B surface antigen (HBsAg) Hepatitis B surface antibody (Anti-HBs) Hepatitis B core total antibody (Anti-HBc) Hepatitis B core IgM antibody Hepatitis B core IgG antibody HBV DNA	Used to evaluate/rule out: Acute or exacerbation of chronic HBV infection.	Utilize a Hepatic Monitoring central lab collection kit and select Hepatitis B
Hepatitis C Virus (HCV) testing: ^{c, d} HCV antibody HCV RNA	Used to evaluate/rule out: Acute or exacerbation of chronic HCV infection.	Utilize a Hepatic Monitoring central lab collection kit and select Hepatitis C
Hepatitis E Virus (HEV) Testing: ^e HEV IgG antibody HEV IgM antibody HEV RNA	Used to evaluate/rule out: Acute HEV infection.	Utilize a Hepatic Monitoring central lab collection kit and select Hepatitis E
Anti-nuclear antibody (ANA) Anti-smooth muscle antibody (ASMA) Anti-actin antibody Immunoglobulin IgA Immunoglobulin IgG Immunoglobulin IgM	Used to evaluate/rule out: Autoimmune hepatitis	Utilize a Hepatic Monitoring central lab collection kit and select only the specific test/s required.
Hepatobiliary imaging: ^{a, h} Ultrasonography Computed tomography scan Magnetic resonance imaging Magnetic resonance cholangiopancreatography (MRCP) ^g Endoscopic retrograde cholangiopancreatography (ERCP) ^g	Used to evaluate/rule out: Biliary obstruction Pancreatitis Gallstones Portal-vein/ hepatic vein thrombosis Hepatic metastasis	Performed locally. If findings are clinically significant, report as an adverse event.
Comprehensive Hepatic Monitoring		
Coagulation: Prothrombin Time, INR (PT-INR)	Used to evaluate/rule out: Suspected liver failure, for patients with elevated Total Bilirubin	Utilize a Hepatic Monitoring central lab collection kit

Epstein-Barr Virus (EBV) Testing: EBV antibody EBV DNA	Used to evaluate/rule out: EBV or	Utilize a Hepatic Monitoring central lab collection kit and select only the specific test/s needed.
Cytomegalovirus (CMV) Testing: CMV antibody CMV DNA	Hepatic injury due to CMV, or	
Herpes Simplex Virus (HSV) Testing: HSV (Type 1 and 2) antibody HSV (Type 1 and 2) DNA	HSV infection.	
Additional Hepatic Monitoring Tests		
Alkaline Phosphatase Isoenzymes	Used to evaluate/differentiate: Elevated Alkaline Phosphatase origination from bone or liver	Utilize a Hepatic Monitoring central lab collection kit
Liver Kidney Microsomal Type 1 (LMK-1) Antibody	Used to evaluate: Autoimmune hepatitis	Utilize a Hepatic Monitoring central lab collection kit
Urine Chemistry: Ethyl glucuronide (EtG) ⁱ Other Chemistry: Phosphatidylethanol (PEth) ^j	Used to evaluate: Alcoholic liver disease	Utilize a Hepatic Monitoring central lab collection kit
Other Chemistry: Acetaminophen Acetaminophen Protein Adducts	Used to evaluate: Acetaminophen toxicity	Utilize a Hepatic Monitoring central lab collection kit
Ethyl Alcohol (EtOH)	Used to evaluate recent alcohol consumption	Utilize a Hepatic Monitoring central lab collection kit
Haptoglobin	Used to evaluate a diagnosis of hemolysis	Utilize a Hepatic Monitoring central lab collection kit
Cardiology consult ^a Electrocardiogram Echocardiogram Vital Signs: Blood pressure Pulse	Used to evaluate: Ischemic or congestive hepatic injury	Performed locally. If findings are clinically significant, report as an adverse event.
Urine Chemistry: Drug screen	Used to evaluate: Hepatotoxicity due to cocaine, opiates and other illicit substances	Utilize a Hepatic Monitoring central lab collection kit
Hepatitis D Virus (HDV) Testing: HDV antibody	Used to evaluate/rule out: Acute HDV infection.	Utilize a Hepatic Monitoring central lab collection kit and only select required test needed.
Microbiology: Cultures: Blood Urine	Used to evaluate/rule out: Sepsis or systemic infection	Perform locally. If findings are clinically significant, report as an adverse event.
Slit-lamp eye examination (Kayser-Fleisher rings) Genetic evaluation	Used to evaluate/rule out: Wilson's disease	Perform locally. If findings are clinically significant, report as an adverse event.

Other Chemistry: Ceruloplasmin Copper	Used to evaluate/rule out: Wilson's disease	Utilize a Hepatic Monitoring central lab collection kit
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*This tool is to be used by the investigative site for reference during the evaluation of a participant who met hepatic monitoring criteria based on laboratory results and clinical judgment for a suspected liver injury during protocol participation.

^a Extent and type of work-up may vary by participant's history, severity of liver injury, underlying disease, and geography.

^b Serum AST typically (although not always) is higher than ALT.

^c If anti-HCV is positive, HCV RNA is required to confirm HCV infection.

^d Acute hepatitis C may be anti-HCV negative but HCV RNA positive.

^e If anti-HEV IgM is positive, consider confirmation with HEV RNA by nested polymerase chain reaction.

^f A liver biopsy is needed to confirm a diagnosis of AIH.

^g If cholestatic injury, MRCP or ERCP may be recommended.

^h Based on medical history and clinical judgment.

ⁱ Alcohol consumption in past 3 to 5 days.

^j Alcohol consumption in past 3 weeks.

10.7. Appendix 7: Abbreviations and Definitions

Term	Definition
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
CFR	Code of Federal Regulations
CI	confidence interval
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
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.
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
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.
GCP	good clinical practice
IB	investigator's brochure
IEC	independent ethics committee
ICF	informed consent form
ICH	International Council for Harmonisation

informed consent	A process by which a participant voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the participant's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
IRB	institutional review board
NSCLC	Non-small cell lung carcinoma
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
PFOS	powder for oral suspension
PK	pharmacokinetics
QTc	corrected QT interval
QTcB	corrected QT interval using Bazett's formula
QTcF	corrected QT interval using Fridericia's formula
QTL	quality tolerance limit
RTU	ready to use
SAE	serious adverse event
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
SoA	schedule of assessments
TBL	total bilirubin
ULN	upper limit of normal

10.8. Appendix 8: Protocol Amendment History

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

Amendment [a]: (07-Sep-2021)

This amendment is considered to be nonsubstantial.

Overall Rationale for the Amendment:

The protocol is amended to correct the timepoints for clinical laboratory assessments in the Schedule of Activities. Minor editorial changes have been done which is not reflected in the below table. The following table describes the change made in amendment (b).

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities (SoA)	<ul style="list-style-type: none"> Added timepoints for collection of PK samples in the table and deleted the following information in the footnotes “Samples will be taken at the following timepoints on Days 1,8 and 15: predose, and 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 12, 24, 36, 48, 72, 96, 120, 144 hours postdose” from footnote of Schedule of Activities (SoA) table for consistent presentation. Added PK sample - Selpercatinib (plasma) timepoint for early discontinuation (ED). 	<ul style="list-style-type: none"> To remove the additional PK sampling timepoints that were inadvertently added in Original Protocol.
1.3 Schedule of Activities (SoA)	<ul style="list-style-type: none"> Added Single 12-lead ECG assessment at ED. 	<ul style="list-style-type: none"> Missing 12-lead ECG assessment added.
1.3 Schedule of Activities (SoA)	<ul style="list-style-type: none"> A comment has been added to the Taste Assessment Questionnaire “To be performed for the RTU suspension and PFOS formulations only immediately after dosing”. 	<ul style="list-style-type: none"> To clarify taste assessment will be measured after dosing.
1.3 Schedule of Activities (SoA)	<ul style="list-style-type: none"> Deleted the foot note “Vital signs assessments on Days 5 and 14 should be performed in the morning at a time relative to 	<ul style="list-style-type: none"> To correct the schedule of activities for the missing vital signs measurement

Section # and Name	Description of Change	Brief Rationale
	<p>predose on Days 1 and 8, respectively”.</p> <ul style="list-style-type: none"> Added “Assessments on Days 5 12, and 19 should be performed in the morning at a time relative to predose on Days 1, 8 and 15, respectively” to the table. Timepoints for vital signs measurement <ul style="list-style-type: none"> added on Day 9, 12, 16 and 19 deleted on Day 14. 	timepoints in the original protocol.
10.2.1 Blood Sampling Summary	<ul style="list-style-type: none"> Added Blood sampling Summary table. 	This summary table was missed in Original Protocol.
10.4.2 Contraception Guidance	<ul style="list-style-type: none"> Added Bilateral tubal occlusion. 	This procedure was inadvertently missed in Original Protocol.

11. References

Levey AS, Stevens LA, Schmid CH, et al. A New Equation to Estimate Glomerular Filtration Rate. *Ann Interim Med.* 2009;150(9):604-612.

LOXO-RET-19075 Clinical Study Report: An Open-Label, 3-Period, Fixed Sequence Study to Evaluate the Effect of an H₂ Antagonist and a Proton Pump Inhibitor on the Single Dose Pharmacokinetics of LOXO-292 in Healthy Adult Subjects

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