Protocol 05 Protocol (c) J2G-MC-JZJZ

# An Open-label, Randomized Study to Evaluate the Bioequivalence of Selpercatinib Formulations

NCT05089019

Approval Date: 14-Oct-2021

# Title Page


## Confidential Information

The information contained in this document is confidential and is intended for the use of clinical investigators. It is the property of Eli Lilly and Company or its subsidiaries and should not be copied by or distributed to persons not involved in the clinical investigation of selpercatinib (LY3527723) unless such persons are bound by a confidentiality agreement with Eli Lilly and Company or its subsidiaries.

**Note to Regulatory Authorities:** This document may contain protected personal data and/or commercially confidential information exempt from public disclosure. Eli Lilly and Company requests consultation regarding release/redaction prior to any public release. In the United States, this document is subject to Freedom of Information Act Exemption 4 and may not be reproduced or otherwise disseminated without the written approval of Eli Lilly and Company or its subsidiaries.


**Protocol Title:** An Open-Label, Randomized Study to Evaluate the Bioequivalence of Selpercatinib Formulations

**Protocol Number:** J2G-MC-JZJZ

**Amendment Number:** (c)

**Compound:** LY3527723

**Brief Title:** A Bioequivalence Study of Selpercatinib Formulations

**Study Phase:** Phase 1

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

**Legal Registered Address:** Indianapolis, Indiana 46285, USA

**Regulatory Agency Identifier Number:**

IND: 133193

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

Approval Date:

Approval Date: 14-Oct-2021 GMT

**Medical Monitor Name and Contact Information will be provided separately.**

## Protocol Amendment Summary of Changes Table

| DOCUMENT HISTORY | |
|---|---|
| **Document** | **Date** |
| Amendment b | 13-Aug-2021 |
| Amendment a | 04-Aug-2021 |
| Original Protocol | 19-Jul-2021 |

### Amendment (c)

This amendment is considered to be nonsubstantial.

### Overall Rationale for the Amendment:

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| Title Page and 1.1 Protocol Synopsis | • Changed the study title and brief title to<br>An Open-Label, Randomized Study to Evaluate the Bioequivalence of Selpercatinib Formulations | • Omit the specificity around formulations |
| 1.1 Synopsis, Overall Design and<br>8.5 Gastric pH | • Included utilization of local anesthetic text | • Facilitate NG insertion |
| 1.1 Synopsis, Number of Participants and<br>Section 9.5 Sample Size Determination | • Updated enrollment to approximately 60 participants for Stage 1 | • Intent is to have at least 50 participants complete Stage 1 |
| 1.3 Schedule of Activities | • Modified visit days for 12-lead ECG, vital signs and clinical laboratory tests | • Align with content in protocol |
| 4.4 End of Study Definition | • Incorporated Day 28 | • Clarify last visit |
| 5.2 Exclusion Criteria | • Included 11. Inadvertent omission of exclusion line item | • Missing Exclusion Criterion 11 |
| 10.2 Appendix 2: Clinical Laboratory Tests | • Incorporated total cholesterol, LDL and HDL | • Response to FDA feedback |

## Table of Contents

**1. Protocol Summary ..... 7**
1.1. Synopsis ..... 7
1.2. Schema ..... 11
1.3. Schedule of Activities (SoA) – Stages 1 and 2 ..... 12

**2. Introduction ..... 16**
2.1. Study Rationale ..... 16
2.2. Background ..... 16
2.3. Benefit/Risk Assessment ..... 17

**3. Objectives and Endpoints ..... 18**

**4. Study Design ..... 19**
4.1. Overall Design ..... 19
4.1.1. Screening ..... 19
4.1.2. Treatment and Assessment Period ..... 19
4.2. Scientific Rationale for Study Design ..... 20
4.3. Justification for Dose ..... 20
4.4. End of Study Definition ..... 21

**5. Study Population ..... 22**
5.1. Inclusion Criteria ..... 22
5.2. Exclusion Criteria ..... 23
5.3. Lifestyle Considerations ..... 25
5.3.1. Meals and Dietary Restrictions ..... 25
5.3.2. Caffeine, Alcohol, and Tobacco ..... 26
5.3.3. Activity ..... 26
5.4. Screen Failures ..... 26

**6. Study Intervention(s) and Concomitant Therapy ..... 27**
6.1. Study Intervention(s) Administered ..... 27
6.1.1. Administration Details ..... 27
6.2. Preparation, Handling, Storage, and Accountability ..... 27
6.3. Measures to Minimize Bias: Randomization and Blinding ..... 28
6.4. Study Intervention Compliance ..... 28
6.5. Dose Modification ..... 28
6.6. Continued Access to Study Intervention After the End of the Study ..... 28
6.7. Treatment of Overdose ..... 28
6.8. Concomitant Therapy ..... 29

**7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal ..... 30**
7.1. Discontinuation of Study Intervention ..... 30
7.1.1. Liver Chemistry Stopping Criteria ..... 30
7.1.2. QTc Stopping Criteria ..... 31
7.2. Participant Discontinuation/Withdrawal from the Study ..... 31
7.3. Lost to Follow-up ..... 32

**8. Study Assessments and Procedures ..... 33**
8.1. Efficacy Assessments ..... 33
8.2. Safety Assessments ..... 33
8.2.1. Physical Examinations ..... 33
8.2.2. Height and Weight ..... 33
8.2.3. Vital Signs ..... 33
8.2.4. Electrocardiograms ..... 34
8.2.5. Clinical Safety Laboratory Tests ..... 34
8.2.6. Pregnancy Testing ..... 34
8.2.7. Safety Monitoring ..... 35
8.3. Adverse Events, Serious Adverse Events, and Product Complaints ..... 37
8.3.1. Timing and Mechanism for Collecting Events ..... 37
8.3.2. Pregnancy ..... 39
8.3.3. Product Complaints ..... 40
8.4. Pharmacokinetics ..... 40
8.5. Gastric pH (Stage 1 only) ..... 41
8.6. Pharmacodynamics ..... 41
8.7. Genetics ..... 41
8.8. Biomarkers ..... 41
8.9. Immunogenicity Assessments ..... 41
8.10. Health Economics ..... 41

**9. Statistical Considerations ..... 42**
9.1. Statistical Hypotheses ..... 42
9.2. Analyses Sets ..... 42
9.2.1. Study Participant Disposition ..... 42
9.2.2. Study Participant Characteristics ..... 42
9.2.3. Treatment Compliance ..... 42
9.3. Statistical Analyses ..... 42
9.3.1. Safety Analyses ..... 42
9.3.2. Pharmacokinetic Analyses ..... 43
9.3.3. Pharmacodynamic Analyses ..... 43
9.3.4. Pharmacokinetic/Pharmacodynamic Analyses ..... 43
9.4. Interim Analysis ..... 43
9.5. Sample Size Determination ..... 44

**10. Supporting Documentation and Operational Considerations ..... 46**
10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations ..... 46
10.1.1. Regulatory and Ethical Considerations ..... 46
10.1.2. Informed Consent Process ..... 46
10.1.3. Data Protection ..... 47
10.1.4. Dissemination of Clinical Study Data ..... 47
10.1.5. Data Quality Assurance ..... 48
10.1.6. Source Documents ..... 49
10.1.7. Study and Site Start and Closure ..... 49
10.1.8. Publication Policy ..... 50

10.2. Appendix 2: Clinical Laboratory Tests....51
10.2.1. Blood Sampling Summary....53
10.3. Appendix 3: Adverse Events and Serious Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting....54
10.3.1. Definition of AE....54
10.3.2. Definition of SAE....55
10.3.3. Definition of Product Complaints....56
10.3.4. Recording and Follow-Up of AE and/or SAE and Product Complaints....56
10.3.5. Reporting of SAEs....58
10.3.6. Regulatory Reporting Requirements....58
10.4. Appendix 4: Contraceptive and Barrier Guidance....60
10.4.1. Definitions....60
10.4.2. Contraception Guidance....60
10.5. Appendix 5: Genetics....63
10.6. Appendix 6: Liver Safety: Suggested Actions and Follow-up Assessments....64
10.7. Appendix 7: Abbreviations and Definitions....69
10.8. Appendix 11: Protocol Amendment History....71

**11. References....73**

# 1. Protocol Summary

## 1.1. Synopsis

**Protocol Title:** An Open-Label, Randomized Study to Evaluate the Bioequivalence of Selpercatinib Formulations

**Brief Title:** A Bioequivalence Study of Selpercatinib Formulations

**Rationale:**
Lilly is developing a tablet formulation in strengths of 40 mg, 80 mg, 120 mg, and 160 mg that will replace the current commercial capsule formulation. The tablets are intended to offer an improved patient experience in terms of the number and size of the dosage units. The intention of this study is to demonstrate the clinical bioequivalence of the new 160 mg tablet formulation of selpercatinib as compared to the current 2 × 80 mg commercial capsule formulation of selpercatinib.

Selpercatinib has pH-dependent solubility, with decreasing solubility at higher pH. This pH-dependent solubility has led to an approximate 69 to 88% reduction (CV% 59.45 to 64.12) in selpercatinib area under the curve (AUC) when selpercatinib was given under fasted conditions to participants treated with the acid-reducing agent omeprazole (proton pump inhibitor).

**Objectives and Endpoints:**

| Objectives | Endpoints |
|---|---|
| Primary | |
| • To evaluate the bioequivalence of a single 160-mg dose of selpercatinib as the tablet formulation (test) compared to the commercial capsule formulation (reference) | • $C_{max}$, AUC(0-∞), and AUC0-$t_{last}$ of selpercatinib |
| Secondary | |
| • To describe the safety and tolerability of a single 160-mg oral dose of selpercatinib as the tablet formulation (test) compared to the commercial capsule formulation (reference) | • Summary of the number of treatment-emergent adverse events and serious adverse events |

**Overall Design:**

Screening

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

Treatment Period

*Stage 1*

Participants will be admitted to the Clinical Research Unit (CRU) on Day -1. On the morning of Day 1, participants will be randomized to receive a single oral dose of 160-mg selpercatinib as the capsule or tablet formulation, and will be dosed according to the randomization sequence following an overnight fast of at least 10 hours. On Day 1, participants will also have an nasal gastric (NG) tube placed in the stomach prior to dosing to assess gastric pH. The NG tube should be inserted into the participant's stomach no more than 60 minutes prior to selpercatinib dosing. The use of local anesthetic (for example, lidocaine) will be allowed to facilitate the insertion of NG tube. Measurements will then be taken at 30 minute intervals for up to 3.5 hours following administration of selpercatinib, or for as long as this remains feasible. The NG tube will be removed from the participant after the 3.5 hour selpercatinib pharmacokinetic (PK) timepoint (i.e., will remain in place for approximately 4 hours after dosing). Participants will remain resident at the CRU until discharge on Day 7.

Participants will attend outpatient visits for the collection of PK blood samples and assessment of vital signs on Days 9 and 11.

Participants will be re-admitted to the CRU on Day 14 and in the morning of Day 15 will receive their second single oral dose of 160-mg selpercatinib as the capsule or tablet formulation, according to the randomization schedule, following an overnight fast of at least 10 hours. On Day 15, participants will also have an NG tube placed in the stomach prior to dosing to assess

gastric pH prior to dosing to assess gastric pH. The NG tube should be inserted into the participant's stomach no more than 60 minutes prior to selpercatinib dosing. The use of local anesthetic (for example, lidocaine) will be allowed to facilitate the insertion of NG tube. Measurements will then be taken at 30 minute intervals for up to 3.5 hours following administration of selpercatinib, or for as long as this remains feasible. The NG tube will be removed from the participant after the 3.5 hour selpercatinib PK timepoint (i.e., will remain in place for approximately 4 hours after dosing). Participants will remain resident at the CRU until discharge on Day 21.

Participants will attend outpatient visits for the collection of blood samples and assessment of vital signs on Days 23, 25, and 28.

There will be a washout of at least 14 days between doses of selpercatinib.

*Stage 2*

Participants will be admitted to the CRU on Day -1. On the morning of Day 1, participants will be randomized to receive a single oral dose of 160-mg selpercatinib as the capsule or tablet formulation, and will be dosed according to the randomization sequence following an overnight fast of at least 10 hours. Participants will remain resident at the CRU until discharge on Day 7.

Participants will attend outpatient visits for the collection of PK blood samples and assessment of vital signs on Days 9 and 11.

Participants will be re-admitted to the CRU on Day 14 and in the morning of Day 15 will receive their second single oral dose of 160-mg selpercatinib as the capsule or tablet formulation, according to the randomization schedule, following an overnight fast of at least 10 hours. Participants will remain resident at the CRU until discharge on Day 21.

Participants will attend outpatient visits for the collection of blood samples and assessment of vital signs on Days 23, 25, and 28.

There will be a washout of at least 14 days between doses of selpercatinib.

**Brief Summary:**

Study JZJZ will be a Phase 1 open-label, randomized, two-period, two-formulation, two-sequence, two-stage adaptive crossover study in adult, heathy, male and female participants, following regulatory guidance. The new 160 mg tablet will be compared to 2 × 80 mg commercially available capsules (160 mg is the highest approved dose).

**Number of Participants:**

The incidence of those participants with a different PK profile (2 of 19 participants in Study LOXO-RET-18015) has meant that Lilly is planning to enroll up to approximately 60 participants in Stage 1. This is to ensure that at least 50 participants will complete Stage 1 and a sufficient variation of gastric pH will be incorporated in Stage 1.

The sample size for Stage 2 will be determined based on data from Stage 1.

In Stage 1, dropouts will not be replaced.

In Stage 2, dropouts will not be replaced, but over-enrollment of up to 20% of the determined sample size will be permitted to ensure a sufficient number of participants.

**Intervention Groups and Duration:**

Participants will participate in 1 stage of the study only. Participants will be screened within 28 days prior to enrollment and will receive and will receive 2 single 160-mg oral doses of selpercatinib separated by a washout of at least 14 days.

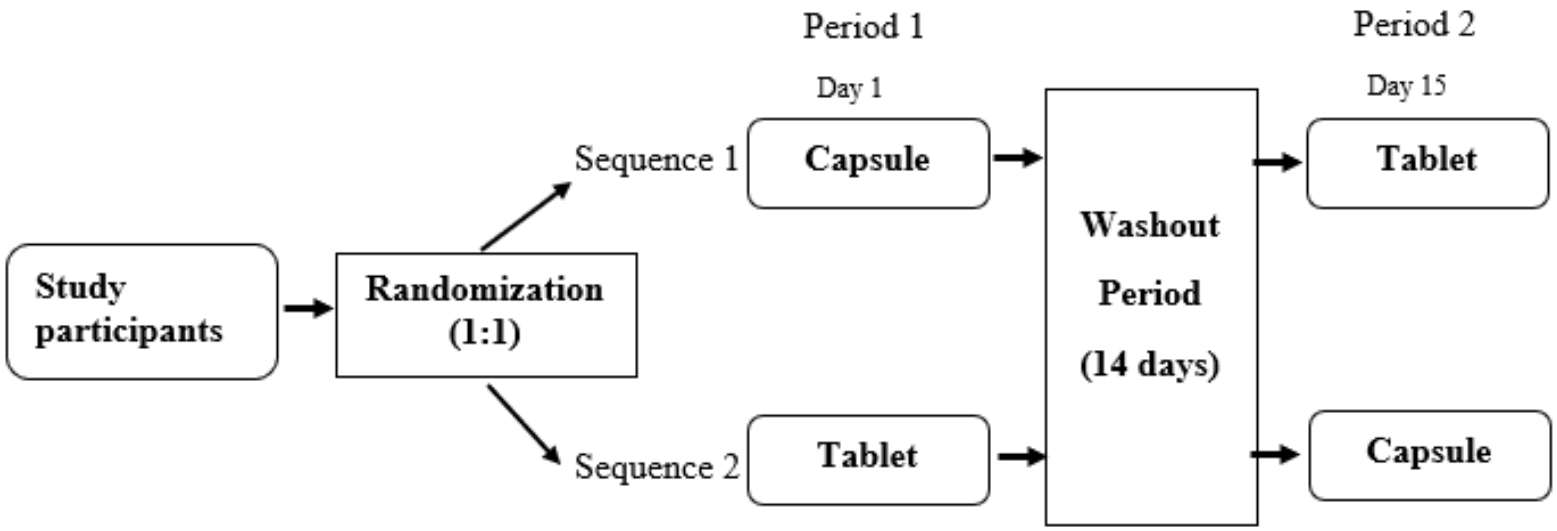
The study duration for participants in each stage of the study is expected to be as follows:

- **Stage 1** = 56 days
- **Stage 2** = 56 days

**Data Monitoring Committee:** No

## 1.2. Schema

**Two by Two Crossover Design (Applicable to Stage 1 and Stage 2)**



## 1.3. Schedule of Activities (SoA) – Stages 1 and 2

| | **Screening** | **Days** | | | | | | | | | | | | | | | | | | | | | **ED** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Procedure** | -28 to -2 days prior to Day 1 | -1 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 9 | 11 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 23 | 25 | 28 | |
| Informed consent | X | | | | | | | | | | | | | | | | | | | | | | |
| Inclusion and exclusion criteria | X | | | | | | | | | | | | | | | | | | | | | | |
| Demography | X | | | | | | | | | | | | | | | | | | | | | | |
| Participant Admission to CRU | | X | | | | | | | | | | X | | | | | | | | | | | |
| Participant Discharge from CRU | | | | | | | | | X | | | | | | | | | | X | | | | |
| Outpatient visit | X | | | | | | | | | X | X | | | | | | | | | X | X | X | X |
| Medical history (includes substance usage [and family history of premature cardiovascular disease])[a] | X | X | | | | | | | | | | | | | | | | | | | | | |
| Past and current medical conditions | X | | | | | | | | | | | | | | | | | | | | | | |
| Height and weight[b] | X | X | | | | | | | | | | | | | | | | | | | | X | X |

| | **Screening** | **Days** | | | | | | | | | | | | | | | | | | | | **ED** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Procedure** | -28 to -2 days prior to Day 1 | -1 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 9 | 11 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 23 | 25 | 28 | |
| Physical examination[c] | | X | | | | | | | | | | X | | | | | | | | | | X | X |
| Serum or urine pregnancy test (women of childbearing potential only)[d] | X | X | | | | | | | | | | X | | | | | | | | | | X | X |
| Follicle-stimulating hormone (postmenopausal women only) | X | | | | | | | | | | | | | | | | | | | | | | |
| Human immunodeficiency virus, hepatitis B and C screen | X | | | | | | | | | | | | | | | | | | | | | | |
| Urine ethanol test | X | X | | | | | | | | | | X | | | | | | | | | | | |
| Urine drug screen | X | X | | | | | | | | | | X | | | | | | | | | | | |
| 12-lead ECG[e] | X | X | P, 2h | | X | | | | | | | | P, 2h | | X | | | | | | | X | X |
| Vital signs (supine)[f] | X | X | P, 1, 2h | 24h | | | | | X | X | X | X | P, 1, 2h | | | | | | X | X | X | X | X |

| | **Screening** | **Days** | | | | | | | | | | | | | | | | | | | | **ED** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Procedure** | -28 to -2 days prior to Day 1 | -1 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 9 | 11 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 23 | 25 | 28 | |
| Clinical laboratory tests (include liver chemistries)[g] | X | X | | 24 h | | | | | X | | | X | | 24 h | | | | | X | | | X | X |
| Genetic sample | | | X | | | | | | | | | | | | | | | | | | | | |
| Gastric pH (Stage 1 only)[h] | | | P, 0.5, 1, 1.5, 2, 2.5, 3, 3.5 h | | | | | | | | | | P, 0.5, 1, 1.5, 2, 2.5, 3, 3.5 h | | | | | | | | | | |
| PK samples - Selpercatinib (plasma) | | | P, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 12 h | 24, 36 h | 48 h | 72 h | 96 h | 120 h | 144 h | X | X | X | P, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 12 h | 24, 36 h | 48 h | 72 h | 96 h | 120 h | 144 h | X | X | X | X |
| Randomization | | | X | | | | | | | | | | | | | | | | | | | | |
| Selpercatinib administration | | | X | | | | | | | | | | X | | | | | | | | | | |
| Adverse event /Serious adverse event review | X | X | ←==========→ | | | | | | | | | | | | | | | | | | | | X |

| | **Screening** | **Days** | | | | | | | | | | | | | | | | | | | | **ED** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Procedure** | -28 to -2 days prior to Day 1 | -1 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 9 | 11 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 23 | 25 | 28 | |
| Concomitant medication review | X | X | ←==========→ | | | | | | | | | | | | | | | | | | | | X |

[a] Full medical history to be taken at screening; interim medical history to be taken at Day -1.

[b] Height to be measured at Screening only.

[c] Full physical examination to be performed at Check-in. Symptom-driven physical examinations to be performed at all other timepoints.

[d] Serum pregnancy test will be performed at screening. Urine pregnancy test will be performed at every admission to the CRU and at poststudy, if applicable.

[e] Single ECGs are required.

[f] Time points may be added, if warranted and agreed upon between Lilly and the investigator.

[g] See Appendix 2 (Section 10.2), Clinical Laboratory Tests, for details.

[h] NG tube placement first pH measurement done prior to dosing (see Section 8.5). The NG tube will be removed from the participant after the 3.5-hour pH timepoint.

# 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 FDA for the treatment of advanced or metastatic RET-mutant Medullary Thyroid Cancer (MTC), and advanced or metastatic RET fusion-positive thyroid cancer, in adults and children ≥12 years; and for the treatment of metastatic RET fusion-positive 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

Lilly is developing a tablet formulation in strengths of 40 mg, 80 mg, 120 mg, and 160 mg that will replace the current commercial capsule formulation. The tablets are intended to offer an improved patient experience in terms of the number and size of the dosage units. The intention of this study is to demonstrate the clinical bioequivalence of the new 160 mg tablet formulation of selpercatinib as compared to the current 2 × 80 mg commercial capsule formulation of selpercatinib.

Selpercatinib has pH-dependent solubility, with decreasing solubility at higher pH. This pH-dependent solubility has led to an approximate 69 to 88% reduction (CV% 59.45 to 64.12) in selpercatinib AUC when selpercatinib was given under fasted conditions to participants treated with the acid-reducing agent omeprazole (proton pump inhibitor).

## 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 or 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. The most frequently reported (≥15% of participants regardless of attribution to study drug) Adverse events (AEs) in the ongoing first-in-human dose finding study were dry mouth, diarrhea, hypertension, AST/ALT increased, fatigue, constipation, edema peripheral, nausea, headache, blood creatinine increased, abdominal pain, rash, ECG QT prolonged, cough, vomiting, and dyspnea.

The median $t_{max}$ of selpercatinib is 2 hours and is slowly eliminated with a mean $t_{1/2}$ of approximately 32 hours in healthy volunteers. More detailed information about the PK and absorption, distribution, metabolism, and excretion properties of selpercatinib may be found in the IB.

## 2.3. Benefit/Risk Assessment

There is no anticipated therapeutic benefit for the 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 160 mg, as it is the highest approved dose. The safety profile of selpercatinib is very well tolerated in healthy volunteers and is clinically manageable, with the low rates of study drug discontinuation due to 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 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 | |
| • To evaluate the bioequivalence of a single 160-mg dose of selpercatinib as the tablet formulation (test) compared to the commercial capsule formulation (reference) | • $C_{max}$, AUC(0-∞), and AUC0-$t_{last}$ of selpercatinib |
| Secondary | |
| • To describe the safety and tolerability of a single 160-mg oral dose of selpercatinib as the tablet formulation (test) compared to the commercial capsule formulation (reference) | • Summary of the number of treatment-emergent AEs and serious adverse events |
| Exploratory | |
| • To determine whether the PK of selpercatinib are altered by initial pH | • $C_{max}$, AUC(0-∞), and $t_{max}$ of selpercatinib |

# 4. Study Design

## 4.1. Overall Design

Study JZJZ will be a Phase 1 open-label, randomized, two-period, two-formulation, two-sequence, two-stage adaptive crossover study in adult heathy male and female participants. The new 160 mg tablet will be compared to 2 × 80 mg commercially available capsules (160 mg is the highest approved dose). The schemata in Section 1.2 illustrate the study randomization and crossover schema.

Exploratory analysis of pH measurements (done via nasal gastric [NG] tube insertion and aspiration of gastric secretions and testing via pH meter) will be included in Stage 1 to understand the pH dynamics, including the potential of pH effect on absorption. The pH will not be measured in Stage 2 of the study.

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

**Stage 1:**

Participants will be admitted to the CRU on Day -1. On the morning of Day 1, participants will be randomized to receive a single oral dose of 160-mg selpercatinib as the capsule or tablet formulation, and will be dosed according to the randomization sequence following an overnight fast of at least 10 hours. On Day 1, participants will have an NG tube placed in the stomach prior to dosing to assess gastric pH, as outlined in Section 8.5. Participants will remain resident at the CRU until discharge on Day 7.

Participants will attend outpatient visits for the collection of PK blood samples and assessment of vital signs on Days 9 and 11.

Participants will be re-admitted to the CRU on Day 14 and in the morning of Day 15 will receive their second single oral dose of 160-mg selpercatinib as the capsule or tablet formulation, according to the randomization schedule, following an overnight fast of at least 10 hours. On Day 15, participants will have an NG tube placed in the stomach prior to dosing to assess gastric pH. Participants will remain resident at the CRU until discharge on Day 21.

Participants will attend outpatient visits for the collection of blood samples and assessment of vital signs on Days 23, 25, and 28.

There will be a washout of at least 14 days between doses of selpercatinib.

**Stage 2:**

Participants will be admitted to the CRU on Day -1. On the morning of Day 1, participants will be randomized to receive a single oral dose of 160-mg selpercatinib as the capsule or tablet

formulation, and will be dosed according to the randomization sequence following an overnight fast of at least 10 hours. Participants will remain resident at the CRU until discharge on Day 7.

Participants will attend outpatient visits for the collection of PK blood samples and assessment of vital signs on Days 9 and 11.

Participants will be re-admitted to the CRU on Day 14 and in the morning of Day 15 will receive their second single oral dose of 160-mg selpercatinib as the capsule or tablet formulation, according to the randomization schedule, following an overnight fast of at least 10 hours. Participants will remain resident at the CRU until discharge on Day 21.

Participants will attend outpatient visits for the collection of blood samples and assessment of vital signs on Days 23, 25, and 28.

There will be a washout of at least 14 days between doses of selpercatinib.

## 4.2. Scientific Rationale for Study Design

A single 160-mg dose of selpercatinib was selected as it is the highest proposed dose for selpercatinib use in adults.

In order to allow each participant to act as his/her own control for safety and PK comparisons, a 2-sequence, 2-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.

The two-stage adaptive design will be used because assumption of intrasubject variability for $C_{max}$ is not well established. Stage 1 PK results will be used to determine intrasubject variability for $C_{max}$ and AUC and the required sample size for Stage 2. Potvin Method C (Potvin 2007) will be used to control the one-sided type I error rate ($\alpha$=0.05) for assessing bioequivalence in 2 stages. (See details in Section 9.4).

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

Selpercatinib has pH-dependent solubility, with decreasing solubility at higher pH; exploratory analysis of pH measurements via NG tube placement, aspiration of gastric secretions and tested on a pH meter will be included in Stage 1 to understand the pH dynamics, including the potential of pH effect on absorption. The pH will not be measured in Stage 2 of the study. Stage 1 is sufficiently sized to ensure that within these normal healthy participants a sufficient range of pH will be detected for the planning of Stage 2 which is planned to fulfill the bioequivalence (BE) guidance for change of delivery option.

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

## 4.3. Justification for Dose

CCI [redacted]

## 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, Day 28 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**

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.
5. Participants who are able to tolerate NG tube placement into the stomach (Stage 1 only).

**Weight**

6. Have a body mass index within the range 19.0 to 35.0 kg/$m^2$ (inclusive).

**Sex and Contraceptive/Barrier Requirements**

7. Male or female

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

a. Male participants:
   - Are not required to adhere to contraceptive requirements

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, vaginal ring, 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**

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

## 5.2. Exclusion Criteria

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

**Medical Conditions**

1. Have a positive pregnancy test at screening or Day -1, where applicable
2. Are planning to become pregnant during the study or within 1 month of study completion
3. Are women who are lactating
4. Have known allergies to selpercatinib-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 QTcB or QTcF >450 msec at screening
8. Have clinically significant active cardiovascular disease or history of myocardial infarction within 6 months prior to the planned start of selpercatinib

9. Have a history or presence of cardiovascular, respiratory, renal, gastrointestinal, endocrine, hematological, or neurological disorders capable of significantly altering the absorption, metabolism, or elimination of drugs; of constituting a risk when taking the investigational product; or of interfering with the interpretation of data. Appendectomy, splenectomy, and cholecystectomy are considered as acceptable
10. Have a creatinine clearance <60 mL/min, as calculated using the CKD-EPI equation (Levey et al, 2009).

$$eGFR = 141 \times \min(Scr/K, 1)^{\alpha} \times \max(Scr/K, 1)^{-1.209} \times 0.993^{age}$$
$$\times 1.018 \text{ (if female)}$$
$$\times 1.159 \text{ (if black)}$$

11. Inadvertent omission of exclusion line item
12. 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
13. Have a history or presence of neuropsychiatric disease (e.g., bipolar disorder, schizophrenia, depression) considered as clinically significant by the investigator
14. Regularly use known drugs of abuse or show positive findings on drug screening
15. Show evidence of human immunodeficiency virus infection and/or positive human immunodeficiency virus antibodies
16. Presence of hepatitis B surface antigen at screening or within 3 months prior to first dose of study intervention
17. 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
18. 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
19. Have donated blood of more than 500 mL within the previous 2 months of study screening
20. Have any medical conditions, medical history, or are taking any medications which are contraindicated in the selpercatinib label

**Prior/Concomitant Therapy**

21. 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.
22. Have previously completed or withdrawn from this study or any other study investigating selpercatinib, and have previously received the investigational product

23. Use of $H_2$ blockers, proton pump inhibitors, and other drugs that affect selpercatinib exposure within 7 days of screening
24. 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)

**Prior/Concurrent Clinical Study Experience**

25. Are currently enrolled in any other clinical study involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study

**Other Exclusions**

26. Have an average weekly alcohol intake that exceeds 21 units per week (males ≤65 years old) 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)
27. 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
28. 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
29. 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).
30. Are unable to consume a standard meal (e.g., breakfast, lunch, dinner, and snack).
31. 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
32. Inability to comply with the dietary regimen of the CRU
33. Are Lilly employees or are an employee of any third-party involved in the study who require exclusion of their employees
34. 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
35. In the opinion of the investigator or sponsor, are unsuitable for inclusion in the study

## 5.3. Lifestyle Considerations

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

### 5.3.1. Meals and Dietary Restrictions

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.

In both Stages 1 and 2 of the study, selpercatinib will be dosed in the fasted state on Day 1 and Day 15.

On 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 during introduction of the NG tube and at dosing. Food is allowed from 4 hours postdose. At all other times during the study, participants may consume water ad libitum.

Foods and beverages containing poppy seeds, grapefruit, or Seville oranges will not be allowed from 7 days prior to check-in until discharge from the study.

### 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 Day -1 until after discharge from the study.

Participants will abstain from alcohol for 48 prior to Day -1 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 JZJZ.6.1. Study Interventions Administered**

| **Study Intervention** | Selpercatinib | Selpercatinib |
|---|---|---|
| **Dosage Formulation** | Capsule | Tablet |
| **Unit Dose Strength/Dosage Level** | 2 × 80-mg capsules (160 mg selpercatinib) | 1 × 160-mg tablets (160 mg selpercatinib) |
| **Route of Administration** | Oral | Oral |
| **Dosing Instructions** | 2 capsules taken on Day 1 or Day 15, according to the randomization schedule | 1 tablet taken on Day 1 or Day 15, according to the randomization schedule |

### 6.1.1. Administration Details

A single oral dose of selpercatinib 160-mg will be administered in the morning of Days 1 and 15 with approximately 240 mL of room temperature water while in a sitting position. Participants will not be allowed to lie supine for 2 hours after dosing, unless clinically indicated or for study procedures.

Selpercatinib capsules and tablets should be swallowed whole. Participants should not break, crush, or chew the capsules or tablets, and should not empty the contents of the capsules.

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.

In both Stages 1 and 2, 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 or tablet on Days 1 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 eCRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention. Study site personnel will examine each participant's mouth to ensure that the study intervention was ingested.

## 6.5. Dose Modification

Dose modification 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 AE/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 study intervention prematurely for any reason should complete AE and other early discontinuation procedures as per the SoA (Section 1.3).

Participants discontinuing from the study prematurely for any reason must complete AE and 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).

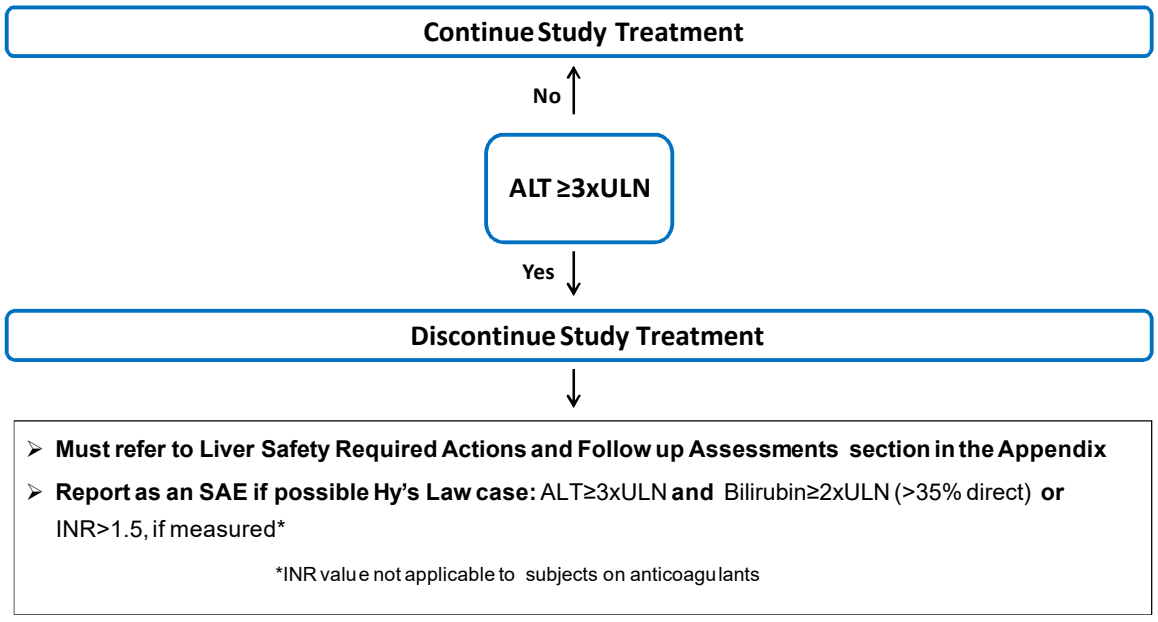
## 7.1. Discontinuation of Study Intervention

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, 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 QTc using Bazett's formula 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 enrollment in any other clinical study involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
- if the participant, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication, discontinuation from the study occurs prior to introduction of the new agent.

Discontinuation is expected to be uncommon.

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA. See SoA for data to be collected at the time of study discontinuation and discharge from the study, 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.

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

### 8.2.2. Height and Weight

Height and weight will be measured and recorded at the times indicated in the SoA (Section 1.3).

### 8.2.3. Vital Signs

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

Blood pressure and pulse rate should be measured 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.

### 8.2.4. 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.

### 8.2.5. 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.

### 8.2.6. Pregnancy Testing

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

### 8.2.7. 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.

#### 8.2.7.1. Hepatic Safety

Close hepatic monitoring

Laboratory tests (Appendix 6 [Section 10.6]), including ALT, AST, alkaline phosphatase (ALP), total bilirubin, 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 × ULN | ALT or AST ≥3 × ULN |
| ALP <1.5 × ULN | ALP ≥2 × ULN |
| TBL <1.5 × ULN | TBL ≥2 × ULN (except for patients with Gilbert's syndrome) |
| ALT or AST ≥1.5 × ULN | ALT or AST ≥2 × baseline |
| ALP ≥1.5 × ULN | ALP ≥2 × baseline |
| TBL ≥1.5 × ULN | TBL ≥2 × 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, history of alcohol drinking and other substance abuse.
Initially, monitoring of symptoms and hepatic biochemical tests should be done at a frequency of 1 to 3 times weekly, based on the participant's clinical condition and hepatic biochemical tests. Subsequently, the frequency of monitoring may be lowered to once every 1 to 2 weeks, if the participant's clinical condition and laboratory results stabilize. Monitoring of ALT, AST, ALP, and TBL should continue until levels normalize or return to approximate baseline levels.

Comprehensive hepatic evaluation

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

| If a participant with baseline results of... | develops the following elevations: |
|---|---|
| ALT or AST <1.5 × ULN | ALT or AST ≥3 × ULN with hepatic signs/symptoms*, or ALT or AST ≥5 × ULN |
| ALP <1.5 × ULN | ALP ≥3 × ULN |
| TBL <1.5 × ULN | TBL ≥2 × ULN (except for patients with Gilbert's syndrome) |
| ALT or AST ≥1.5 × ULN | ALT or AST ≥2 × baseline with hepatic signs/symptoms*, or ALT or AST ≥3 × baseline |
| ALP ≥1.5 × ULN | ALP ≥2 × baseline |
| TBL ≥1.5 × ULN | TBL ≥1.5 × 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 ≥5 × ULN on 2 or more consecutive blood tests (if baseline ALT <1.5 × ULN)
   - In participants with baseline ALT ≥1.5 × ULN, the threshold is ALT ≥3 × baseline on 2 or more consecutive tests
2. Elevated TBL to ≥2 × ULN (if baseline TBL <1.5 × ULN) (except for cases of known Gilbert's syndrome)
   - In participants with baseline TBL ≥1.5 × ULN, the threshold should be TBL ≥2 × baseline
3. Elevation of serum ALP to ≥2 × ULN on 2 or more consecutive blood tests (if baseline ALP <1.5 × ULN)
   - In participants with baseline ALP ≥1.5 × ULN, the threshold is ALP ≥2 × baseline on 2 or more consecutive blood tests
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 informed consent form (ICF) | participation in study has ended | As soon as possible upon site awareness | AE eCRF | N/A |
| **Serious Adverse Event** | | | | | |
| SAE and SAE updates – prior to start of study intervention **and** deemed reasonably possibly related with study procedures | signing of the informed consent form (ICF) | start of intervention | Within 24 hours of awareness | SAE paper form | SAE paper form |

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

| Event | Collection Start | Collection Stop | Timing for Reporting to Sponsor or Designee | Mechanism for Reporting | Back-up Method of Reporting |
|---|---|---|---|---|---|
| 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 10.1. 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 Committees (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 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. Gastric pH (Stage 1 only)

In Stage 1, at the time points specified in the SoA (Section 1.3), on dosing days prior to selpercatinib dosing, participants will have a NG tube inserted into the stomach. The NG tube should be inserted into the participant's stomach no more than 60 minutes prior to selpercatinib dosing. The use of local anesthetic (for example, lidocaine) will be allowed to facilitate the insertion of NG tube. CCI

If for some reason the participant does not tolerate the NG tube after the initial pH reading, the tube can be removed and this would not be considered a protocol violation. If gastric secretions are not able to be aspirated at any timepoint after the initial pH measurement, this is not considered a protocol violation.

The pH measurement data will be added to the eCRF.

## 8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

## 8.7. 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.

## 8.8. Biomarkers

Biomarkers are not evaluated in this study.

## 8.9. Immunogenicity Assessments

Not applicable for this study.

## 8.10. Health Economics

This section is not applicable for this study.

# 9. Statistical Considerations

## 9.1. Statistical Hypotheses

The primary objective will be evaluated to assess the bioequivalence of the tablet formulation compared to the capsule formulation.

## 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 IP 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 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: $C_{max}$, AUC(0-∞), AUC0-$t_{last}$, and $t_{max}$.

Other noncompartmental parameters, such as $t_{1/2}$, apparent total body clearance of drug calculated after extravascular administration, and apparent volume of distribution during the terminal phase after extravascular administration, may be reported as appropriate.

#### 9.3.2.2. Pharmacokinetic Statistical Inference

Pharmacokinetic parameters will be evaluated to estimate bioequivalence. For the primary analysis, log-transformed $C_{max}$, AUC0-$t_{last}$, and AUC(0-∞) 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 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

The pH data will be listed and summarized using descriptive statistics.

### 9.3.4. Pharmacokinetic/Pharmacodynamic Analyses

Not applicable for this study.

## 9.4. Interim Analysis

At completion of Stage 1, an interim analysis will be conducted to test BE and estimate the power before continuing to Stage 2.

In order to meet the BE criterion at a specific α level, the 2-sided confidence interval for the tablet-to-capsule (tablet formulation / capsule formulation) geometric mean ratio (GMR) for

AUC and $C_{max}$ at the (1-2α) level should fall within 80%-125%. The sequential design approach of Potvin's Method C will be used to preserve the overall type I error rate at the 1-sided significance level of 0.05.

The BE testing and alpha spending scheme is described in Figure JZJZ.9.1. At an interim analysis, the power will be evaluated using the intrasubject CV from Stage 1 using α level of 0.05 assuming the true tablet-to-capsule GMR is 1.05. If Stage 1 has at least 90% power, BE will be tested at Stage 1 at an α level of 0.05. The study will be stopped whether BE is met or not met. The evaluation of the power at Stage 1 will be based on $C_{max}$, which has higher variability. If the power is less than 90%, BE will be tested at an α level of 0.0294 as originally proposed by Pocock (Pocock 1977). If the BE criterion is met, the study will be stopped. If the BE criterion is not met, the sample size for Stage 2 will be calculated based on the intrasubject CV at Stage 1 and an α level of 0.0294 assuming the true tablet-to-capsule GMR is 1.05, and Stage 2 will be initiated. At Stage 2, BE will be evaluated using data from both stages at an α level of 0.0294.

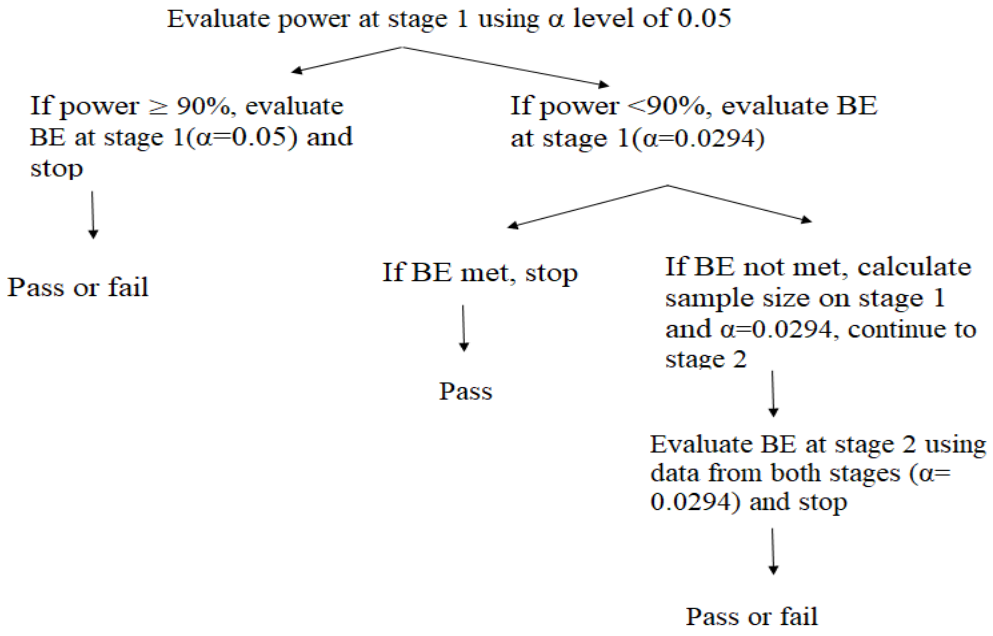



**Figure JZJZ.9.1. Adaptive sequential design method C (Potvin, 2007).**

The Statistical Analysis Plan will describe the planned interim analyses in greater detail.

## 9.5. Sample Size Determination

The incidence of those participants with a different PK profile (2 of 19 subjects in Study LOXO-RET-18015) has meant that Lilly is planning to enroll up to approximately 60 participants in Stage 1. This is to ensure that at least 50 participants will complete Stage 1 and a sufficient variation of gastric pH will be incorporated in Stage 1.

If the true intraparticipant CV is 30% for $C_{max}$ and 20% for AUC, the first 50 participants in Stage 1 will give approximately 90% power to meet BE criteria at a 1-sided α level of 0.05, under an assumption of a GMR of 1.05.

Table JZJZ.9.1 shows the required sample size for Stage 2 to provide the power for $C_{max}$ of 90% based on different intrasubject CV for $C_{max}$ from Stage 1, assuming the true tablet-to-capsule GMR is 1.05 under scenario when the power is less than 90% and BE is not met at Stage 1. The actual sample size for Stage 2 will be determined based on the observed intrasubject CV at Stage 1.

In Stage 1, dropouts will not be replaced.

In Stage 2, dropouts will not be replaced, but over-enrollment of up to 20% of the determined sample size will be permitted to ensure a sufficient number of participants.

**Table JZJZ.9.1. Sample Size for Stage 2 Based on Intrasubject CV for $C_{max}$ in Stage 1**

| **Intrasubject CV for $C_{max}$ in Stage 1** | **Required Sample Size for Stage 2** |
|---|---|
| 40% | 50 |
| 50% | 100 |
| 60% | 156 |
| 70% | 216 |

Abbreviations: $C_{max}$ = maximum serum concentration; CV = coefficient of variation.

Note: The total sample size will be at least 50 for Stage 1 plus the required sample size for Stage 2.

# 10. Supporting Documentation and Operational Considerations

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

### 10.1.1. Regulatory and Ethical Considerations

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

### 10.1.2. 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 which 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 case report forms (CRFs) unless transmitted to the sponsor or designee electronically (for example, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- 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 CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for the time period outlined in the Clinical Trial Agreement unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.
- In addition, sponsor or its representatives will periodically check a sample of the participant data recorded against source documents at the study site. The study may be audited by sponsor or its representatives, and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

**Data Capture System**

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

Data collected via the sponsor-provided data capture system will be stored at third-party. The investigator will have continuous access to the data during the study and until decommissioning of the data capture system. Prior to decommissioning, the investigator will receive 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 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 10.1.5.

### 10.1.7. Study and Site Start and Closure

**First Act of Recruitment**

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

**Study or Site Termination**

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

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

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

For study termination:

- Discontinuation of further study intervention development

For site termination:

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

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

### 10.1.8. Publication Policy

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

## 10.2. Appendix 2: Clinical Laboratory Tests

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

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

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

Investigators must document their review of the laboratory safety results.

### 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 |
| | Total cholesterol, LDL-C, and HDL-C |
| **Differential WBC (absolute counts) of** | Blood urea nitrogen (BUN) |
| Neutrophils | Uric acid |
| Lymphocytes | Gamma-glutamyl transferase (GGT) |
| Monocytes | Total protein |
| Eosinophils | Albumin |
| Basophils | Total bilirubin |
| | Alkaline phosphatase (ALP) |
| **Urinalysis[a]** | Aspartate aminotransferase (AST) |
| Specific gravity | Alanine aminotransferase (ALT) |
| pH | Creatinine |
| Protein | |
| Glucose | Ethanol testing[b] |
| Ketones | Urine drug screen[b] |
| Bilirubin | Hepatitis B surface antigen[c] |
| Urobilinogen | Hepatitis C antibody[c, d] |
| Blood | HIV[c] |
| Nitrite | Pregnancy test (women of childbearing potential only) |
| Leukocyte esterase | FSH (if applicable)[c, e] |

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

[a] Performed by dipstick. Microscopic examination to be performed if dipstick is abnormal for blood, protein, nitrites, or leukocyte esterase.

[b] Urine drug screen and ethanol (urine) level performed at screening and check-in.

[c] Performed at screening only.

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

[e] Postmenopausal women 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-JZJZ Sampling Summary (Stages 1 and 2)**

| Purpose | Blood Volume per Sample (mL) | Maximum Number of Blood Samples | Maximum Total Volume (mL) |
|---|---|---|---|
| Screening tests[a] | 45 | 1 | 45 |
| Clinical laboratory tests[a] | 12 | 8 | 96 |
| CCI | [redacted] | [redacted] | [redacted] |
| Blood discard for cannula patency | 1 | 1 | 1 |
| Genetic sample | 10 | 1 | 10 |
| Total | | | 244 |
| Total for clinical purposes | | | 252 |

[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).<br>• Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.<br>• New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study.<br>• Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.<br>• Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. |

| **Events <u>NOT</u> Meeting the AE Definition** |
|---|
| • Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.<br>• 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.<br>• 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:**

**a. Results in death**

**b. Is life-threatening**

The term *life-threatening* in the definition of *serious* refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

**c. Requires inpatient hospitalization or prolongation of existing hospitalization**

- In general, hospitalization signifies that the participant has been admitted to hospital or emergency ward (usually involving at least an overnight stay) for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

**d. Results in persistent disability/incapacity**

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (for example, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

**e. Is a congenital anomaly/birth defect**

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

**f. Other situations:**

- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as important medical

events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

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

### 10.3.3. Definition of Product Complaints

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

**Assessment of Intensity**

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories:

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

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

**Assessment of Causality**

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship/
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the IB 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 sponsor or designee. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to sponsor or designee.
- The investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

**Follow-up of AEs and SAEs**

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

### 10.3.5. Reporting of SAEs

**SAE Reporting via Paper Form**

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

### 10.3.6. Regulatory Reporting Requirements

**SAE Regulatory Reporting**

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

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

## 10.4. Appendix 4: Contraceptive and Barrier Guidance

### 10.4.1. Definitions

**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. Female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy
   - Documented bilateral tubal ligation
   - Documented 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 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 oral contraceptives, vaginal ring, 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 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 8.2.7.1 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, INR (PT-INR) | Haptoglobin |
| **Serology** | Immunoglobulin IgA (Quantitative) |
| Hepatitis A Virus (HAV) Testing: | Immunoglobulin IgG (Quantitative) |
| HAV Total Antibody | Immunoglobulin IgM (Quantitative) |
| HAV IgM Antibody | Phosphatidylethanol (PEth) |
| Hepatis B Virus (HBV) Testing: | **Urine Chemistry** |
| Hepatitis B surface antigen (HBsAg) | Drug Screen |
| Hepatitis B surface antibody (Anti-HBs) | Ethyl glucuronide (EtG) |
| Hepatitis B core total antibody (Anti-HBc) | **Other Serology** |
| Hepatitis B core IgM antibody | Anti-nuclear antibody (ANA) |
| Hepatitis B core IgG antibody | Anti-smooth muscle antibody (ASMA) [a] |
| HBV DNA [d] | Anti-actin antibody [b] |
| Hepatis 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:**<br>Total bilirubin<br>Direct bilirubin<br>Alkaline phosphatase (ALP)<br>Alanine aminotransferase (ALT)<br>Aspartate aminotransferase (AST) [b]<br>Gamma-glutamyl transferase (GGT)<br>Creatine kinase (CK) | All: Routine follow-up<br><br><br><br><br><br>CK: Muscle injury/rhabdomyolysis | Utilize a Hepatic Monitoring central lab collection kit and select Clinical Chemistry |
| **Hematology**<br>Hemoglobin<br>Hematocrit<br>Erythrocytes (RBCs – Red Blood Cells)<br>Leukocytes (WBCs – White Blood Cells)<br>Differential:<br>Neutrophils, segmented<br>Lymphocytes<br>Monocytes<br>Basophils<br>Eosinophils<br>Platelets<br>Cell Morphology (RBCs and WBCs) | Infection | Utilize a Hepatic Monitoring central lab collection kit and select Hematology |
| **Medical history:** [a, h]<br>Symptoms<br>Co-existing medical conditions<br>Concomitant medications<br>Dietary and nutritional supplements<br>Exercise (excessive)<br>Muscle Injury<br>Alcohol consumption<br>Illicit substances | Used to evaluate/rule out:<br>Systemic infection or sepsis<br>Ischemic or congestive hepatic injury<br>Gallstone disease<br>Alcoholic liver disease<br>Muscle injury/rhabdomyolysis<br>Acetaminophen toxicity<br>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:**<br>HAV Total Antibody<br>HAV IgM Antibody | Used to evaluate/rule out: Acute HAV infection | Utilize a Hepatic Monitoring central lab collection kit and select Hepatitis A |
| **Hepatis B Virus (HBV) Testing:**<br>Hepatitis B surface antigen (HBsAg)<br>Hepatitis B surface antibody (Anti-HBs)<br>Hepatitis B core total antibody (Anti-HBc)<br>Hepatitis B core IgM antibody<br>Hepatitis B core IgG antibody<br>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 |
| **Hepatis C Virus (HCV) testing:** [c, d]<br>HCV antibody<br>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]<br>HEV IgG antibody<br>HEV IgM antibody<br>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)<br>Anti-smooth muscle antibody (ASMA)<br>Anti-actin antibody<br>Immunoglobulin IgA<br>Immunoglobulin IgG<br>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]<br>Ultrasonography<br>Computed tomography scan<br>Magnetic resonance imaging<br>Magnetic resonance cholangiopancreatography (MRCP) [g]<br>Endoscopic retrograde cholangiopancreatography (ERCP) [g] | Used to evaluate/rule out:<br>Biliary obstruction<br>Pancreatitis<br>Gallstones<br>Portal-vein/ hepatic vein thrombosis<br>Hepatic metastasis | Performed locally.<br>If findings are clinically significant, report as an adverse event. |
| **Comprehensive Hepatic Monitoring** | | |
| **Coagulation:**<br>Prothrombin Time, INR (PT-INR) | Used to evaluate/rule out:<br>Suspected liver failure, for patients with elevated Total Bilirubin | Utilize a Hepatic Monitoring central lab collection kit |
| **Epstein-Barr Virus (EBV) Testing:**<br>EBV antibody<br>EBV DNA<br>**Cytomegalovirus (CMV) Testing:**<br>CMV antibody<br>CMV DNA<br>**Herpes Simplex Virus (HSV) Testing:**<br>HSV (Type 1 and 2) antibody<br>HSV (Type 1 and 2) DNA | Used to evaluate/rule out:<br>EBV or<br><br>Hepatic injury due to CMV, or<br><br>HSV infection. | Utilize a Hepatic Monitoring central lab collection kit and select only the specific test/s needed. |
| Liver biopsy [f] | Used to evaluate/rule out:<br>Autoimmune hepatitis (AIH) | If findings are clinically significant, report as an adverse event. |
| **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:**<br>Ethyl glucuronide (EtG) [i]<br>**Other Chemistry:**<br>Phosphatidylethanol (PEth) [j] | Used to evaluate: Alcoholic liver disease | Utilize a Hepatic Monitoring central lab collection kit |
| **Other Chemistry:**<br>Acetaminophen<br>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]<br>Electrocardiogram<br>Echocardiogram<br>Vital Signs:<br>Blood pressure<br>Pulse | Used to evaluate: Ischemic or congestive hepatic injury | Performed locally.<br>If findings are clinically significant, report as an adverse event. |
| **Urine Chemistry:**<br>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:**<br>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:**<br>Cultures:<br>Blood<br>Urine | Used to evaluate/rule out:<br>Sepsis or systemic infection | Perform locally.<br>If findings are clinically significant, report as an adverse event. |
| Slit lamp eye examination (Kayser-Fleisher rings)<br>Genetic evaluation | Used to evaluate/rule out:<br>Wilson's disease | Perform locally.<br>If findings are clinically significant, report as an adverse event. |
| **Other Chemistry:**<br>Ceruloplasmin<br>Copper | Used to evaluate/rule out:<br>Wilson's disease | Utilize a Hepatic Monitoring central lab collection kit |

*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 |
|---|---|
| **ALT** | alanine aminotransferase |
| **AST** | aspartate aminotransferase |
| **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. |
| **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. |
| **DMC** | data monitoring committee. A data monitoring committee, or data monitoring board (DMB) is a group of independent scientists who are appointed to monitor the safety and scientific integrity of a human research intervention, and to make recommendations to the sponsor regarding the stopping of a study for efficacy, or for harms, or for futility. The composition of the committee is dependent upon the scientific skills and knowledge required for monitoring the particular study. |
| **ECG** | Electrocardiogram |
| **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 |
| **ICF** | informed consent form |
| **ICH** | International Council for Harmonisation |
| **IMP** | Investigational Medicinal Product |
| **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. |
| **interim analysis** | An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created/locked. |

| | |
|---|---|
| **investigational product** | A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form. |
| **ITT** | intention to treat: The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a participant (that is, the planned treatment regimen) rather than the actual treatment given. It has the consequence that participant allocated to a treatment group should be followed up, assessed, and analyzed as members of that group irrespective of their compliance to the planned course of treatment. |
| **participant** | Equivalent to CDISC term “subject”: an individual who participates in a clinical trial, either as recipient of an investigational medicinal product or as a control |
| **PC** | product complaint |
| **PK/PD** | pharmacokinetics/pharmacodynamics |
| **PPS** | per-protocol set: The set of data generated by the subset of participant who sufficiently complied with the protocol to ensure that these data would be likely to exhibit the effects of treatment, according to the underlying scientific model. |
| **QTc** | corrected QT interval |
| **SAE** | serious adverse event |
| **SAP** | statistical analysis plan |
| **screen** | The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study. |
| **TEAE** | Treatment-emergent adverse event: An untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment. |

## 10.8. Appendix 11: Protocol Amendment History

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

**Amendment a: 04-August-2021**

**Overall Rationale for the Amendment:**

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| 1.1 Synopsis and 4.1.2 Treatment and Assessment Period | Study design amended to move last outpatient visit from Day 27 to Day 28. | To extend the treatment period by 1 day in order to accommodate a longer PK sampling profile to match Stage 1 and Stage 2 PK sampling. |
| 1.3 Schedule of Activities (SoA) – Stages 1 and 2 | Study design amended to move last outpatient visit from Day 27 to Day 28. | To extend the treatment period by 1 day in order to accommodate a longer PK sampling profile to match Stage 1 and Stage 2 PK sampling. |

**Amendment b: 13-August-2021**

**Overall Rationale for the Amendment:**

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| 1.3 Schedule of Activities (SoA) – Stages 1 and 2 | • PK samples - Selpercatinib (plasma) amended to remove 168, 192, 216, and 240 hours postdose on Days 1 and 15.<br>• Added PK samples - Selpercatinib (plasma) timepoints in tabular format and deleted the information "Samples will be taken at the following timepoints on Days 1 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.<br>• Added gastric pH (Stage 1 only) timepoints in tabular format and deleted the information "Measurements will be taken at the following timepoints on Days 1 and 15: predose, and 0.5, 1, 1.5, 2, 2.5, | • PK samples - Selpercatinib (plasma) timepoints were inadvertently added in previous versions of protocol (Original and amendment a) which have been corrected in current Protocol Amendment (b).<br>• Final safety assessments were inadvertently missed in the table. |

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| | 3, and 3.5 hours postdose" from footnote of SoA table for consistent presentation.<br>• Added final safety assessments on Day 28: physical examination, weight, pregnancy test, 12-lead ECG, vital signs, and clinical laboratory tests | |
| 10.2.1 Blood Sampling Summary | • Maximum number of blood Samples for clinical laboratory tests were updated to reflect changes in SoA for final safety assessments on Day 28. | Final safety assessments on Day 28 were added to SoA – Stages 1 and 2. |
| 11 References | • Added reference "Levey et al, 2009". | This reference was inadvertently missed in the previous versions of protocol (Original and amendment a). |

# 11. References

Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate [published correction appears in Ann Intern Med. 2011 Sep 20;155(6):408]. *Ann Intern Med*. 2009;150(9):604-612. https://doi.org/ 10.7326/0003-4819-150-9-200905050-00006.

Pocock SJ. Group sequential methods in the design and analysis of clinical trials. *Biometrika* 1977; 64:191–199.

Potvin D, DiLiberti CE, Hauck WW, Parr AF, Schuirmann DF, Smith RA. Sequential design approaches for bioequivalence studies with crossover designs. *Pharmaceut. Statist.* 2007, https://doi.org/10.1002/pst.294.

Leo Document ID = 2bebe097-d0b4-4370-afec-7f5614ffe1cb

Approver: PPD

Approval Date & Time: 14-Oct-2021 14:51:58 GMT

Signature meaning: Approved

Approver: PPD

Approval Date & Time: 14-Oct-2021 15:04:58 GMT

Signature meaning: Approved