Protocol J2G-MC-JZJV (a)

An Open-Label Study to Investigate the Effect of Selpercatinib on the Pharmacokinetics of Dabigatran in Healthy Volunteers

NCT04782076

Approval Date: 05-Mar-2021

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

Protocol Number: J2G-MC-JZJV

Amendment Number: (a)

Compound: LY3527723

Study Phase: Phase 1

Short Title: A DDI Study of Selpercatinib and Dabigatran in Healthy Volunteers

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

Legal Registered Address: Indianapolis, Indiana 46285 USA

Regulatory Agency Identifier Number(s):

IND: 133193

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

Approval Date: 05-Mar-2021 GMT

Medical Monitor Name and Contact Information will be provided separately.

Table of Contents

1. Protocol Summary

1.1. Synopsis

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

Short Title: A DDI Study of Selpercatinib and Dabigatran in Healthy Volunteers

Rationale:

The P-gp is a membrane-bound, efflux transporter located in the small intestine, colon, and liver (among other tissues), serving to limit the absorption of drugs from the gastrointestinal tract and to increase biliary secretion of drugs and their metabolites. Certain substrates of P-gp have been shown to have clinically significant drug interactions when administered with inhibitors of P-gp (International Transporter Consortium et al. 2010).

This study aims to evaluate the safety, tolerability, and PK of dabigatran in the presence of selpercatinib. Dabigatran is a sensitive substrate of the efflux transporter P-gp (FDA Clinical DDI Guidance, 2020). Selpercatinib is an inhibitor of P-gp in vitro; an effect of selpercatinib on P-gp in the intestine cannot be ruled out. Based on the pH-dependent solubility of selpercatinib, the potential gut concentrations of selpercatinib are higher under fed conditions compared to under fasted conditions. Therefore, this study is designed to address the potential effect of selpercatinib on P-gp in the intestine under fed conditions to account for the worst scenario of selpercatinib inhibition.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To evaluate the effect of selpercatinib on P-gp activity in healthy participants	• C_{max} and AUC(0-∞) of dabigatran to assess P-gp activity
Secondary	
• To evaluate the safety and tolerability of dabigatran in combination with selpercatinib in healthy participants • To evaluate the pharmacokinetics of selpercatinib	• Summary of the number of treatment-emergent adverse events and serious adverse events • C_{max}, AUC(0-∞), and t_{max} of selpercatinib

Overall Design:

Screening

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

Treatment and Assessment Period

Eligible participants will take part in 1 treatment period. Participants will be admitted to the CRU on Day -1 and remain resident in the CRU until discharge on Day 11. All participants will receive a single dose of 150 mg dabigatran on Day 1 and a single dose of 150 mg dabigatran coadministered with a single dose of 160 mg selpercatinib on Day 8. There will be a washout period of 7 days between dosing on Days 1 and 8.

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

Follow-up

Participants will return to the CRU for a safety follow-up visit within 14 to 17 days after the final dose.

Disclosure Statement: This is a Phase 1, fixed-sequence, open-label study in healthy participants.

Number of Participants:

Up to 40 participants will be enrolled to ensure that at least 30 evaluable participants complete.

Intervention Groups and Duration:

This is a single-group study, consisting of single oral doses of dabigatran (Day 1) and single oral doses of dabigatran and selpercatinib (Day 8).

Dabigatran/Selpercatinib	
Day 1	Day 8
Dabigatran (150 mg)	Dabigatran (150 mg) + Selpercatinib (160 mg)

A single oral dose of dabigatran etexilate 150 mg will be administered in the morning of Day 1. On the morning of Day 8, a single dose of dabigatran etexilate 150 mg and selpercatinib 160 mg will be administered orally 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.

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.

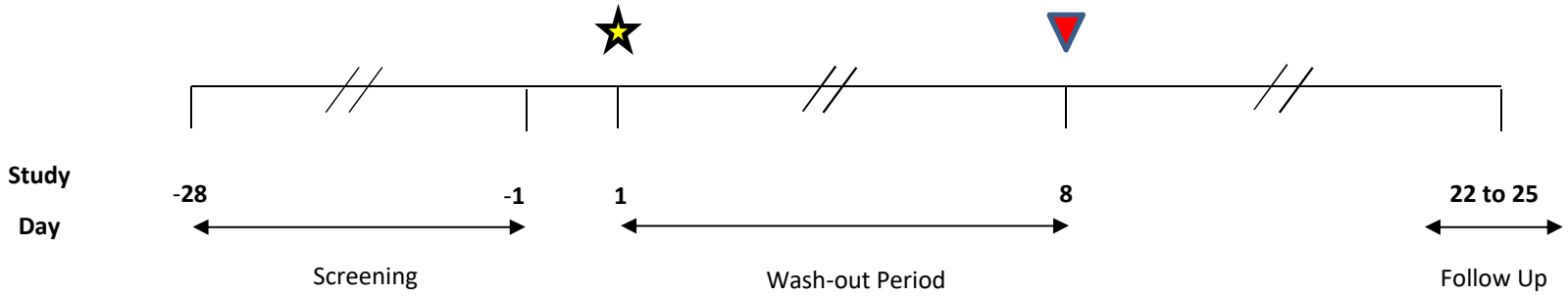
Dabigatran and selpercatinib will be administered with food using a standardized unit meal.

The macronutrient composition of the standardized meals for dabigatran and selpercatinib administration should be targeted to provide approximately 50% of the calories from carbohydrates, 15% protein, and 35% fat. The total calories for the standardized meal to be consumed with each dose is expected to be approximately 685 calories.

Participants will consume the standardized meal 30 minutes prior to administration of study intervention and participants should eat this meal in 30 minutes or less. No additional food should be allowed for at least 4 hours after drug administration.

Data Monitoring Committee: No

1.2. Schema



Dabigatran 150 mg

Dabigatran 150 mg + Selpercatinib 160 mg

1.3. Schedule of Activities (SoA)

	Screening	Days												Follow-Up/ED	Comments
Procedure	-28 to -2 days prior to Day 1	-1	1	2	3	4	5	6	7	8	9	10	11	Within 14 to 17 days after final dose	
Informed consent	X														
Inclusion and exclusion criteria	X														
Demography	X														
Participant Admission to CRU		X													
Participant Discharge from CRU													X		
Outpatient visit	X													X	
Medical history (includes substance usage [and family history of premature cardiovascular disease])	X														
Past and current medical conditions	X														
Physical examination	X	X											X	X	Full physical examination (including height and weight) to be performed at screening.

	Screening	Days											Follow-Up/ED	Comments
Procedure	-28 to -2 days prior to Day 1	-1	1	2	3	4	5	6	7	8	9	10	11	Within 14 to 17 days after final dose	
															Symptom-driven physical examinations to be performed at all other timepoints.
Serum or urine pregnancy test (women of childbearing potential only)	X	X							X					X	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.
Human immunodeficiency virus, hepatitis B and C screen	X														
Urine or breath ethanol test	X	X													
Urine drug screen	X	X													
12-lead ECG	X		P, 2h		X					P, 2h		X			Single ECGs are required.
Vital signs (supine)	X	X	P, 1, 2h	24h					X	P, 1, 2h	24h			X	Time points may be added, if warranted and agreed upon

	Screening	Days											Follow-Up/ED	Comments
Procedure	-28 to -2 days prior to Day 1	-1	1	2	3	4	5	6	7	8	9	10	11	Within 14 to 17 days after final dose	
															between Lilly and the investigator.
Clinical laboratory tests (include liver chemistries)	X	X		24h					X		24h			X	See Appendix 10.2, Clinical Laboratory Tests, for details.
Genetic sample			X												
PK samples - Dabigatran (plasma)			P, 0.5, 1, 2, 3, 4, 6, 8, 10, 12h	24, 36h	48h	72h				P, 0.5, 1, 2, 3, 4, 6, 8, 10, 12h	24, 36h	48h	72h		
PK samples - Selpercatinib (plasma)										P, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12h	24, 36h	48h	72h		

	Screening	**Days**											**Follow-Up/ED**	**Comments**
Procedure	-28 to -2 days prior to Day 1	-1	1	2	3	4	5	6	7	8	9	10	11	Within 14 to 17 days after final dose	
Selpercatinib administration										X					
Dabigatran administration			X							X					
Adverse event /Serious adverse event review	X	X	←==========→											X	
Concomitant medication review	X	X	←==========→											X	

2. Introduction

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

2.1. Study Rationale

The P-gp is a membrane-bound, efflux transporter located in the small intestine, colon, and liver (among other tissues), serving to limit the absorption of drugs from the gastrointestinal tract and to increase biliary secretion of drugs and their metabolites. Certain substrates of P-gp have been shown to have clinically significant drug interactions when administered with inhibitors of P-gp (International Transporter Consortium et al. 2010).

This study aims to evaluate the safety, tolerability, and PK of dabigatran in the presence of selpercatinib. Dabigatran is a sensitive substrate of the efflux transporter P-gp (FDA Clinical DDI Guidance, 2020). Selpercatinib is an inhibitor of P-gp in vitro; an effect of selpercatinib on P-gp in the intestine cannot be ruled out. Based on the pH-dependent solubility of selpercatinib, the potential gut concentrations of selpercatinib are higher under fed conditions compared to under fasted conditions. Therefore, this study is designed to address the potential effect of selpercatinib on P-gp in the intestine under fed conditions to account for the worst scenario of selpercatinib inhibition.

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, 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) 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.

Dabigatran etexilate, a competitive, direct thrombin inhibitor, is a P-gp substrate. Following absorption, dabigatran etexilate is hydrolyzed to form dabigatran, the active moiety. Dabigatran concentrations reach t_{max} within 2 hours of administration, and then concentrations decline in a biphasic manner, with a terminal $t_{1/2}$ of 12 to 17 hours. Dabigatran is primarily eliminated through renal excretion and does not appear to be a substrate for renal transporters based on the reported renal clearance of 89 mL/min (Stangier 2008). Dabigatran itself is not a substrate for the cytochrome P450 family of metabolizing enzyme nor a substrate for P-gp, meaning that changes in dabigatran exposure following administration of a P-gp inhibitor would be anticipated to only reflect the activity of the inhibition of dabigatran etexilate transport at the intestinal wall (Stangier 2008). Previous studies have investigated the effect of P-gp inhibitors on dabigatran PK. Dabigatran AUC increased by 58% and 53% when coadministered with amiodarone and quinidine, respectively (Pradaxa® Prescribing Information). Ketoconazole, a strong P-gp inhibitor, increased dabigatran AUC and C_{max} values by 138% and 135%, respectively, after a single dose of 400 mg, and 153% and 149%, respectively, after multiple daily 400-mg doses (Pradaxa® Prescribing Information).

2.3. Benefit/Risk Assessment

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

The dose of selpercatinib to be given in this study is 160 mg, as it is the highest approved dose. 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 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.

The dabigatran dose to be administered in this study (150 mg) is within the therapeutic range (see Section 4.3), and has previously been administered to healthy volunteers with no tolerability concerns in other DDI studies (e.g., I8D-MC-AZEE; NCT02568397).

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 effect of selpercatinib on P-gp activity in healthy participants	• C_{max} and AUC(0-∞) of dabigatran to assess P-gp activity
Secondary	
• To evaluate the safety and tolerability of dabigatran in combination with selpercatinib in healthy participants • To evaluate the pharmacokinetics of selpercatinib	• Summary of the number of treatment-emergent adverse events and serious adverse events • C_{max}, AUC(0-∞), and t_{max} of selpercatinib

4. Study Design

4.1. Overall Design

This is a Phase 1, fixed-sequence, open-label study in healthy participants that will study dabigatran P-gp DDI with selpercatinib. The anticipated study duration for each individual participant is approximately 8 weeks.

Screening

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

Treatment and Assessment Period

Eligible participants will take part in 1 treatment period. Participants will be admitted to the CRU on Day -1 and remain resident in the CRU until discharge on Day 11. All participants will receive a single dose of 150 mg dabigatran on Day 1 and a single dose of 150 mg dabigatran coadministered with a single dose of 160 mg selpercatinib on Day 8. There will be a washout period of 7 days between dosing on Days 1 and 8.

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

Follow-up

Participants will return to the CRU for a safety follow-up visit within 14 to 17 days after the final dose.

4.2. Scientific Rationale for Study Design

A single 160-mg dose of selpercatinib was selected as it is the highest approved 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 fixed sequence design has been selected. This study will also be open-label as the study primary endpoint PK measures are objective rather than subjective.

Based on the $t_{1/2}$ of dabigatran, a period of 7 days between dabigatran doses is considered sufficient time for the study drug to washout.

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

4.3. Justification for Dose

Dabigatran etexilate is currently approved in the United States to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation, for the treatment of deep

venous thrombosis and pulmonary embolism, and to reduce the risk of recurrence of deep venous thrombosis and pulmonary embolism (Pradaxa Prescribing Information). The recommended dose for dabigatran etexilate is 150 mg twice daily for patients with creatinine clearance >30 mL/min (Praxada Prescribing Information). Single oral doses of 10 to 400 mg dabigatran etexilate have been administered to healthy participants and were well tolerated (Stangier et al. 2008). There is a possibility of an interaction of dabigatran etexilate with selpercatinib and the dose selected allows for this possibility. The selected 150 mg dose for this study should provide adequate plasma dabigatran concentrations to address the study objectives with minimal risk for AEs (Härtter et al. 2013).

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

The doses will be administered at approximately the same time on Day 1 and Day 8. The actual time of dose administrations will be recorded in the participant's electronic CRF.

4.4. End of Study Definition

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

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

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 ICF.

Type of Participant

2. Participants who are overtly healthy as determined by medical evaluation including medical history, physical examination, and vital signs.
3. Participants who have clinical laboratory test results within the normal reference range for the population or investigative site, or results with acceptable deviations that are judged to be not clinically significant by the investigator.
4. Participants who have venous access sufficient to allow for blood sampling as per the protocol.

Weight

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

Sex

6. Male or female

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

Male participants:

- are not required to adhere to contraceptive requirements

Female participants:

- Female participants of childbearing potential (see Appendix 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 or oral contraceptives, implanted/injected contraceptives, intrauterine devices, or sterile partner until 30 days after the last dose of study medication.
    - Female participants not of childbearing potential are not required to use contraception. This includes females who are:
        - Infertile due to surgical sterilization (hysterectomy, bilateral oophorectomy, bilateral salpingectomy, or tubal ligation) or congenital anomaly (for example, Müllerian agenesis)
        - Postmenopausal as defined in Appendix 10.4.

Informed Consent

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

5.2. Exclusion Criteria

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

Medical Conditions

1. Have a positive pregnancy test at screening or Day -1, where applicable
2. Are planning to become pregnant during the study or within 1 month of study completion
3. Are women who are lactating
4. Have known allergies to selpercatinib- or dabigatran-related compounds or any components of the formulation of selpercatinib or dabigatran, or history of significant atopy
5. Have a history of allergic reactions to medications or food products
6. Have a clinically significant abnormality of blood pressure and/or pulse rate as determined by the investigator
7. Have known bleeding disorder including prior personal or familiar history of abnormal bleeding, hereditary or acquired coagulation or platelet disorder, or abnormal coagulation test (prothrombin time/international normalized ratio or partial thromboplastin time/activated partial thromboplastin time greater than ULN) result at screening

8. Clinically significant abnormalities on ECG as determined by the investigator or prolongation of the QTcB or QTcF >450 msec on more than 1 ECG obtained at screening
9. Have clinically significant active cardiovascular disease or history of myocardial infarction within 6 months prior to the planned start of selpercatinib
10. 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
11. Have a creatinine clearance <60 mL/min, as calculated using the CKD-EPI equation (Levey et al, 2009).

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

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., manic depressive illness, 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 antibody RNA test is obtained
18. Positive hepatitis C antibody 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 dabigatran 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 H2 blockers, proton pump inhibitors, and other drugs that affect dabigatran and/or 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. Consume excessive amounts of coffee, tea, cola, or other caffeinated beverages per day, or are unwilling to stop caffeine consumption 48 hours prior to admission and whilst 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.
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.

Dabigatran and selpercatinib will be administered with food using a standardized unit meal.

The macronutrient composition of the standardized meals for dabigatran and selpercatinib administration should be targeted to provide approximately 50% of the calories from carbohydrates, 15% protein, and 35% fat. The total calories for the standardized meal to be consumed with each dose is expected to be approximately 685 calories. Subjects will be encouraged to eat the entire meal.

Each component of the meal will be weighed separately and documented in grams pre and post meal to determine the percentage of the meal consumed in grams by the subject. The nutritional intake will be documented in grams and recorded in the electronic case report form (eCRF).

Participants will complete the standardized meal 30 minutes prior to administration of study intervention and participants should eat this meal in 30 minutes or less. No additional food should be allowed for at least 4 hours after drug administration.

5.3.2. Caffeine, Alcohol, and Tobacco

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

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

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

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 Interventions Administered

Table JZJV.1. Study Interventions Administered

Study Intervention	Selpercatinib	Dabigatran etexilate
Dosage Formulation	Capsule	Capsule
Unit dose strength(s)/Dosage Level(s)	2 × 80-mg capsules (160 mg selpercatinib)	150-mg capsule
Route of Administration	Oral	Oral
Dosing Instructions	2 capsules taken on Day 8	1 capsule taken on Day 1 and 1 capsule taken on Day 8

6.1.1. Administration Details

A single oral dose of dabigatran etexilate 150 mg will be administered in the morning of Day 1 with approximately 240 mL of room temperature water while in a sitting position. On the morning of Day 8, a single dose of dabigatran etexilate 150 mg and selpercatinib 160 mg will be administered orally 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.

Dabigatran etexilate and selpercatinib capsules should be swallowed whole. Participants should not break, crush, chew, or empty the contents of either capsule.

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

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature 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 and only authorized site staff may supply 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 site staff.

3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
4. The investigator or designee will return all unused study interventions to Lilly or its designee at the end of the study. In some cases, sites may destroy the material if, during the CRU selection, the evaluator has verified and documented that the site has appropriate facilities and written procedures to dispose of clinical materials.

6.3. Measures to Minimize Bias: Randomization and Blinding

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

6.4. Study Intervention Compliance

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

6.5. Concomitant Therapy

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

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

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

Participants must abstain from taking prescription or nonprescription drugs (including vitamins and dietary or herbal supplements) within 14 days 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 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.

6.6. Dose Modification

Dose modification is not permitted in this study.

6.7. Intervention after the End of the Study

Not applicable.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

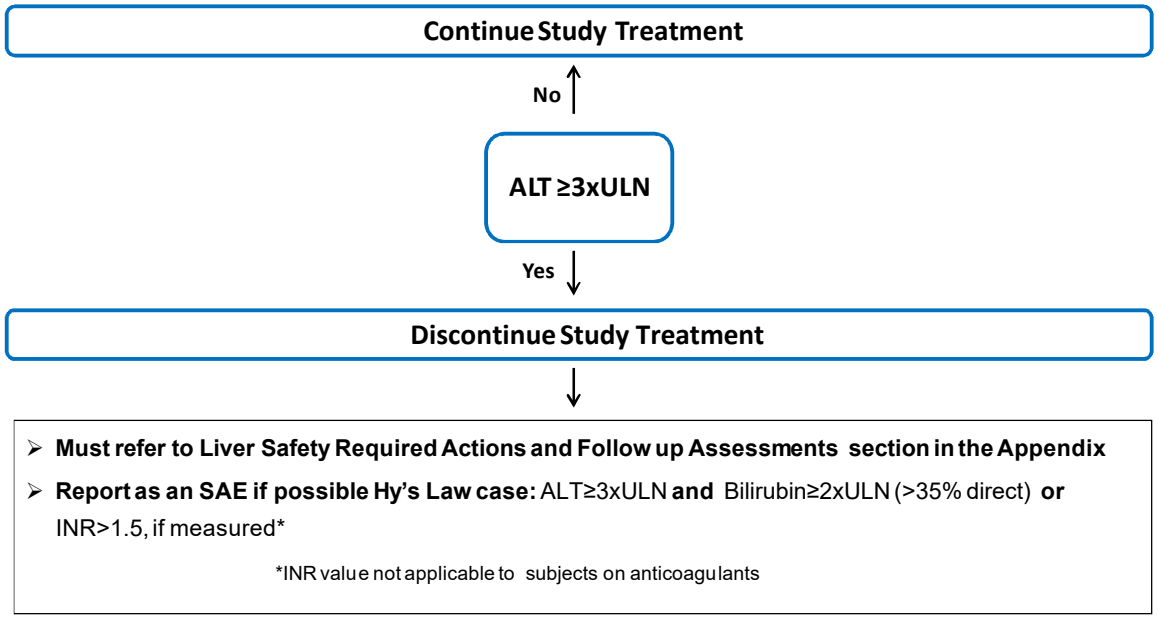
Participants discontinuing from the study prematurely for any reason must complete and follow-up procedures per Section 1.3 of this protocol.

7.1. Discontinuation of Study Intervention

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

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 10.6.

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 follow-up and for any further evaluations that need to be completed.

7.2. Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the study:

- at any time at his/her own request
- at the request of his/her designee (for example, parents or legal guardian)
- 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

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 the SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed. The participant will be permanently discontinued both from the study intervention and from the study at that time.

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

7.2.1. Discontinuation of Inadvertently Enrolled Participants

If the sponsor or investigator identify a participant who did not meet enrollment criteria and was inadvertently enrolled, then the participant should be discontinued from study treatment unless there are extenuating circumstances that make it medically necessary for the participant to continue on study treatment. If the investigator and the sponsor CRP agree it is medically appropriate to continue, the investigator must obtain documented approval from the sponsor CRP to allow the inadvertently enrolled participant to continue in the study with or without treatment with investigational product. Safety follow-up is as outlined in Section 1.3 (Schedule of

Activities), Section 8.2 (Safety Assessments), and Section 8.3 (Adverse Events and Serious Adverse Events) of the protocol.

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. Site personnel are expected to make diligent attempts to contact participants who fail to return for a scheduled visit or were otherwise unable to be followed up by the site.

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

8. Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.
- 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.

8.2. Safety Assessments

8.2.1. Physical Examinations

- Physical examinations should be conducted according to the SoA (Section 1.3).
- A full physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems. Height and weight will also be measured and recorded.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.2. Vital Signs

- For each participant, vital signs measurements should be conducted according to the SoA (Section 1.3).
- Blood pressure and pulse rate should be measured singly after at least 5 minutes supine. For each individual participant, the same cuff size should be used throughout the study for the measurements of blood pressure. The cuff should be attached to the participant's dominant arm.
- Unscheduled orthostatic vital signs should be assessed, if possible, during any AE of dizziness or posture-induced symptoms. Where orthostatic measurements are required, participants should be supine for at least 5 minutes and then participants will stand, and standing blood pressure will be measured after 2 minutes, but no longer than 3 minutes. If

the participant feels unable to stand, supine vital signs only will be collected. Additional vital signs may be measured if warranted.

8.2.3. Electrocardiograms

- For each participant, single 12-lead ECGs will be obtained as outlined in the SoA (see Section 1.3). Refer to Section 7 for QTc withdrawal criteria and any additional QTc readings that may be necessary.
- Electrocardiograms must be recorded before collecting any blood samples. Participants must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection. Electrocardiograms may be obtained at additional times, when deemed clinically necessary. All ECGs recorded should be stored at the investigational site.
- Electrocardiograms will be interpreted by the investigator at the site as soon after the time of ECG collection as possible, and ideally while the participant is still present, to determine whether the participant meets entry criteria at the relevant visit(s) and for immediate participant management, should any clinically relevant findings be identified.
- If a clinically significant finding is identified (including, but not limited to, changes in QT/QTc interval from baseline) after enrollment, the investigator will determine if the participant can continue in the study. The investigator, or qualified designee, is responsible for determining if any change in participant management is needed and must document his/her review of the ECG printed at the time of collection. Any new clinically relevant finding should be reported as an AE.

8.2.4. Clinical Safety Laboratory Assessments

- See Appendix 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 10.2, must be conducted in accordance with the laboratory manual and the SoA.

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

8.2.5. Safety Monitoring

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

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

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

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

8.2.5.1. Hepatic Safety

Close hepatic monitoring

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

If a participant with baseline results of ...	develops the following elevations:
ALT or AST <1.5 × 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 and Serious Adverse Events

Product Complaints are covered in Section 8.3.6.

Adverse 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 the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention (see Section 7).

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

All SAEs will be collected from the signing of the ICF until participation in the study has ended.

All AEs will be collected from the start of intervention until the follow-up visit.

Medical occurrences that begin before the start of study intervention but after signing of the ICF will be recorded on the Adverse Event eCRF.

Although all AEs after signing the ICF are recorded by the site in the eCRF/electronic data entry, SAE reporting to the sponsor begins after the participant has signed the ICF and has received study drug. However, if an SAE occurs after signing the ICF, but prior to receiving selpercatinib, it needs to be reported ONLY if it is considered reasonably possibly related to study procedures.

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 10.3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 10.3.

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

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Appendix 10.3.

8.3.4. Regulatory Reporting Requirements for SAEs

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

8.3.5. Pregnancy

- Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected after the start of study intervention and until the follow-up visit.
- If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 10.3.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.
- Pregnancy (maternal or paternal exposure to investigational product) does not meet the definition of an AE. However, to fulfill regulatory requirements, any pregnancy should be reported following the SAE process described in Appendix 10.4 to collect data on the outcome for both mother and fetus.

8.3.6. 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 product complaints 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 8.3.3 and Appendix 10.3 of the protocol.

8.3.6.1. Time Period for Detecting Product Complaints

- Product complaints that result in an AE will be detected, documented, and reported to the sponsor during all periods of the study in which the drug is used.
- If the investigator learns of any product complaint at any time after a participant has been discharged from the study, and such incident is considered reasonably related to a drug provided for the study, the investigator will promptly notify the sponsor.

8.3.6.2. Prompt Reporting of Product Complaints to Sponsor

- Product complaints will be reported to the sponsor within 24 hours after the investigator becomes aware of the complaint.
- The Product Complaint Form will be sent to the sponsor by email. If email is unavailable, then fax should be utilized.

8.3.6.3. Follow-up of Product Complaints

- Follow-up applies to all participants, including those who discontinue study intervention.
- The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the product complaint.
- New or updated information will be recorded on the originally completed form with all changes signed and dated by the investigator and submitted to the sponsor.

8.3.6.4. Regulatory Reporting Requirements for Product Complaints

- As required by local regulations, the investigator will report to their IRB/IEC any unanticipated adverse device effect or unanticipated problem that resulted in an SAE, or any product complaint that could have led to an SAE had precautions not been taken.

8.4. Treatment of Overdose

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

The antidote to dabigatran is idarucizumab and may be used in case of overdose.

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/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.
4. In the case of emergency uncontrolled bleeding as a direct consequence of dabigatran, urgent referral for treatment with idarucizumab should be considered.

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

8.5. Pharmacokinetics

- At the times and visits specified in the SoA, venous blood samples of approximately 2 mL each will be collected to determine the plasma concentrations of selpercatinib and dabigatran.
- A maximum of 3 samples may be collected at additional time points during the study if warranted and agreed upon between the investigator and the sponsor.
- Instructions for the collection and handling of biological samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

8.5.1. Bioanalysis

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

Concentrations of selpercatinib and dabigatran will be assayed using a validated liquid chromatography with tandem mass spectrometry method.

Bioanalytical samples collected to measure investigational product concentrations will be retained for a maximum of 1 year following last participant visit for the study.

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 10.5 for information regarding genetic research and Appendix 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 variables will be evaluated to assess the potential drug-drug interaction. All tests and/or estimation statistics will not be confirmatory but will contribute to a body of evidence to support final conclusions.

9.2. Sample Size Determination

Approximately [redacted] CCI will be enrolled so that approximately [redacted] CCI complete the study. To evaluate the effect of selpercatinib on P-gp activity, it is important that the ratio of geometric means is estimated with reasonable precision. [redacted] CCI

[redacted]

9.3. Populations for Analyses

The following populations are defined:

Population	Description
Entered	All participants who sign the ICF.
Enrolled/Intent-to-Treat	All participants assigned to treatment, regardless of whether they take any doses of investigational product, or if they take the correct treatment.
Safety	All participants assigned to dabigatran and who take at least 1 dose.
Pharmacokinetic Analysis	All participants who received at least 1 dose of dabigatran and have evaluable PK.

9.3.1. Study Participant Disposition

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

9.3.2. Study Participant Characteristics

The participant's age, sex, and other demographic characteristics will be recorded and summarized. Demographic characteristics may be considered in the interpretation of PK and safety analyses.

9.3.3. Treatment Compliance

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

9.4. 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 the investigational product and have evaluable PK.

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

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

9.4.1. Safety Analyses

9.4.1.1. Clinical Evaluation of Safety

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

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

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

9.4.1.2. Statistical Evaluation of Safety

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

9.4.2. Pharmacokinetic Analyses

9.4.2.1. PK Parameter Estimation

Pharmacokinetic parameter estimates will be calculated by standard noncompartmental methods. The primary PK parameters for analysis of dabigatran will be: C_{max} and AUC(0-∞). Other noncompartmental parameters, such as t_{max}, $t_{1/2}$, 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. Noncompartmental PK parameters will also be calculated for selpercatinib.

9.4.2.2. PK Statistical Inference

Pharmacokinetic parameters will be evaluated to estimate DDI for dabigatran. Log-transformed C_{max} and AUC(0-∞) parameters for dabigatran will be evaluated separately. [redacted] CCI [redacted]

Pharmacokinetic parameters will be summarized using descriptive statistics.

9.4.3. Pharmacodynamic Analyses

Not applicable for this study.

9.4.4. Pharmacokinetic/Pharmacodynamic Analyses

Not applicable for this study.

9.5. Interim Analyses

No interim analyses are planned for this study. If an unplanned interim analysis is deemed necessary for reasons other than a safety concern, the protocol must be amended.

9.6. Data Monitoring Committee

No data monitoring committee is required for this study.

10. Supporting Documentation and Operational Considerations

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

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
    - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
    - Applicable ICH GCP Guidelines
    - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., 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.
- 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 the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations
- Investigator sites are compensated for participation in the study as detailed in the clinical trial agreement.

10.1.2. Financial Disclosure

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

10.1.3. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act 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 re-consented 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 or the participant's legally authorized representative and is kept on file.

10.1.4. Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records, datasets, or tissue samples that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that 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 their 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.

10.1.5. Dissemination of Clinical Study Data

Communication of Suspended or Terminated Dosing

If a decision is taken to suspend or terminate dosing in the study due to safety findings, this decision will be communicated by Lilly to all investigators (for example, by phone and/or email) as soon as possible. It will be a requirement that investigators respond upon receipt to confirm

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

Reports

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

Data

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

10.1.6. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic eCRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., contract research organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for the time period outlined in the clinical trial agreement unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.
- In addition, the sponsor or its representatives will periodically check a sample of the participant data recorded against source documents at the study site. The study may be audited by the sponsor or its representatives, and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.
- To ensure accurate, complete, and reliable data, Lilly or its representatives will do the following:
    - provide instructional material to the study sites, as appropriate.
    - provide training to instruct the investigators and study coordinators. This training will give instruction on the protocol, the completion of the eCRFs, and study procedures.
    - make periodic visits to the study site.
    - be available for consultation and stay in contact with the study site personnel by mail, telephone, or fax.

Data Capture System

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

An electronic data capture system will be used in this study for the collection of eCRF data. The investigator maintains a separate source for the data entered by the investigator or designee into the sponsor-provided electronic data capture system. The investigator is responsible for the identification of any data to be considered source and for the confirmation that data reported are accurate and complete by signing the eCRF.

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

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

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

10.1.7. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the electronic CRF 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.

10.1.8. Study and Site Start and Closure

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

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:

- 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 of participants by the investigator
- Discontinuation of further study intervention development

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 ensures appropriate participant therapy and/or follow-up.

10.1.9. Publication Policy

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

10.1.10. Long-Term Sample Retention

Sample retention enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in the development of selpercatinib.

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

*Retention periods may differ locally.

The sponsor has a right to retain a portion of submitted biopsy tissue. Archival blocks will be returned to the study site. Slides and tissue samples collected on study will not be returned.

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed 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.
- Pregnancy testing will be conducted as detailed in the SoA (Section 1.3).

Investigators must document their review of each laboratory safety report.

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
Coagulation	
Prothrombin time (PT)	
Activated partial thromboplastin time (aPTT)	
International normalized ratio (INR)	
Differential WBC (absolute counts) of	Blood urea nitrogen (BUN)
Neutrophils	Uric acid
Lymphocytes	
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)
	FSH (if applicable)[c]

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

[a] Performed by dipstick.

[b] Urine drug screen and ethanol (urine or breath) level performed at screening, and may be repeated prior to admission to the clinical research unit.

[c] Performed at screening only.

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

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-JZJV Sampling Summary

Purpose	Blood Volume per Sample (mL)	Number of Blood Samples	Total Volume (mL)
Screening tests[a]	45	1	45
Clinical laboratory tests[a]	12	5	60
Pharmacokinetics - Selpercatinib	2	15	30
Pharmacokinetics - Dabigatran	2	28	56
Blood discard for cannula patency	1	1	1
Genetic sample	10	1	10
Total			202
Total for clinical purposes			210

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

10.3. Appendix 3: 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 patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdose 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 which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • Medical or surgical procedure (e.g., 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

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:

Results in death

Is life-threatening

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

Requires inpatient hospitalization or prolongation of existing hospitalization

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

Results in persistent disability/incapacity

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

Is a congenital anomaly/birth defect

Other situations:

- Medical or scientific judgment should be exercised 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. Recording and Follow-up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the eCRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the sponsor or designee in lieu of completion of the AE/SAE eCRF page.
- There may be instances when copies of medical records for certain cases are requested by the sponsor or designee. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the sponsor or designee.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. 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 1 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.
- 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.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to the sponsor or designee. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor or designee.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor or designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the originally completed eCRF.
- The investigator will submit any updated SAE data to the sponsor or designee within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting via Paper CRF
• Facsimile transmission of the SAE paper CRF 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. • The investigator or site must alert the Lilly CRP/CP, or its designee, of any SAE as soon as practically possible. Additionally, the investigator or site must alert Lilly Global Patient Safety, or its designee, of any SAE within 24 hours of investigator awareness of the event via a sponsor-approved method. If alerts are issued via telephone, they are to be immediately followed with official notification on study-specific SAE forms. This 24-hour notification requirement refers to the initial SAE information and all follow-up SAE information.

10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

Definitions:

Woman of Childbearing Potential

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

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

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

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

   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)

Contraception Guidance:

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

Male participants:

- are not required to adhere to contraceptive requirements

Female participants:

- Female participants of childbearing potential who are abstinent (if this is complete abstinence, as their preferred and usual lifestyle) or in a same sex relationship (as part of

their preferred and usual lifestyle) must agree to either remain abstinent or stay in a same sex relationship without sexual relationships with males. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence just for the duration of a study, and withdrawal are not acceptable methods of contraception.

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

Collection of Pregnancy Information

Male participants with partners who become pregnant

- The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive study intervention.

- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported including fetal status (presence or absence of anomalies) and indication for the procedure.

Female participants who become pregnant

- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a participant's pregnancy.

- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate, and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, including fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion (occurring at <20 weeks gestational age) or still birth (occurring at >20 weeks gestational age) is always considered to be an SAE and will be reported as such.
- Any poststudy pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.3.4. 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 or advanced or metastatic RET-mutant MTC/advanced or metastatic RET fusion-positive thyroid cancer/metastatic RET fusion-positive NSCLC. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome or analysis of the entire genome (as appropriate).
- Additional analyses may be conducted if it is hypothesized that this may help further understand the clinical data.
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to selpercatinib or study interventions of this class to understand study disease or related conditions.
- The results of genetic analyses may be reported in the clinical study report 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: Required Actions and Follow-up Assessments

Hepatic Evaluation Testing – Refer to protocol Hepatic Safety Section 8.2.5.1 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: Total bilirubin Direct bilirubin Alkaline phosphatase (ALP) Alanine aminotransferase (ALT) Aspartate aminotransferase (AST) [b] Gamma-glutamyl transferase (GGT) Creatine kinase (CK)	All: Routine follow-up CK: Muscle injury/rhabdomyolysis	Utilize a Hepatic Monitoring central lab collection kit and select Clinical Chemistry
Hematology Hemoglobin Hematocrit Erythrocytes (RBCs – Red Blood Cells) Leukocytes (WBCs – White Blood Cells) Differential: Neutrophils, segmented Lymphocytes Monocytes Basophils Eosinophils Platelets Cell Morphology (RBCs and WBCs)	Infection	Utilize a Hepatic Monitoring central lab collection kit and select Hematology
Medical history: [a, h] Symptoms Co-existing medical conditions Concomitant medications Dietary and nutritional supplements Exercise (excessive) Muscle Injury Alcohol consumption Illicit substances	Used to evaluate/rule out: Systemic infection or sepsis Ischemic or congestive hepatic injury Gallstone disease Alcoholic liver disease Muscle injury/rhabdomyolysis Acetaminophen toxicity Drug Induced Liver Injury (DILI) due to another drug, herbal or dietary substances	If findings are clinically significant, report as an adverse event.
Hepatitis A Virus (HAV) Testing: HAV Total Antibody HAV IgM Antibody	Used to evaluate/rule out: Acute HAV infection	Utilize a Hepatic Monitoring central lab collection kit and select Hepatitis A
Hepatis B Virus (HBV) Testing: Hepatitis B surface antigen (HBsAg) Hepatitis B surface antibody (Anti-HBs) Hepatitis B core total antibody (Anti-HBc) Hepatitis B core IgM antibody Hepatitis B core IgG antibody HBV DNA	Used to evaluate/rule out: Acute or exacerbation of chronic HBV infection.	Utilize a Hepatic Monitoring central lab collection kit and select Hepatitis B

Hepatis C Virus (HCV) testing: [c, d] HCV antibody HCV RNA	Used to evaluate/rule out: Acute or exacerbation of chronic HCV infection.	Utilize a Hepatic Monitoring central lab collection kit and select Hepatitis C
Hepatitis E Virus (HEV) Testing: [e] HEV IgG antibody HEV IgM antibody HEV RNA	Used to evaluate/rule out: Acute HEV infection.	Utilize a Hepatic Monitoring central lab collection kit and select Hepatitis E
Anti-nuclear antibody (ANA) Anti-smooth muscle antibody (ASMA) Anti-actin antibody Immunoglobulin IgA Immunoglobulin IgG Immunoglobulin IgM	Used to evaluate/rule out: Autoimmune hepatitis	Utilize a Hepatic Monitoring central lab collection kit and select only the specific test/s required.
Hepatobiliary imaging: [a, h] Ultrasonography Computed tomography scan Magnetic resonance imaging Magnetic resonance cholangiopancreatography (MRCP) [g] Endoscopic retrograde cholangiopancreatography (ERCP) [g]	Used to evaluate/rule out: Biliary obstruction Pancreatitis Gallstones Portal-vein/ hepatic vein thrombosis Hepatic metastasis	Performed locally. If findings are clinically significant, report as an adverse event.
Comprehensive Hepatic Monitoring		
Coagulation: Prothrombin Time, INR (PT-INR)	Used to evaluate/rule out: Suspected liver failure, for patients with elevated Total Bilirubin	Utilize a Hepatic Monitoring central lab collection kit
Epstein-Barr Virus (EBV) Testing: EBV antibody EBV DNA **Cytomegalovirus (CMV) Testing:** CMV antibody CMV DNA **Herpes Simplex Virus (HSV) Testing:** HSV (Type 1 and 2) antibody HSV (Type 1 and 2) DNA	Used to evaluate/rule out: EBV or Hepatic injury due to CMV, or 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: 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: Ethyl glucuronide (EtG) [i] **Other Chemistry:** Phosphatidylethanol (PEth) [j]	Used to evaluate: Alcoholic liver disease	Utilize a Hepatic Monitoring central lab collection kit

Other Chemistry: Acetaminophen Acetaminophen Protein Adducts	Used to evaluate: Acetaminophen toxicity	Utilize a Hepatic Monitoring central lab collection kit
Ethyl Alcohol (EtOH)	Used to evaluate recent alcohol consumption	Utilize a Hepatic Monitoring central lab collection kit
Haptoglobin	Used to evaluate a diagnosis of hemolysis	Utilize a Hepatic Monitoring central lab collection kit
Cardiology consult [a] Electrocardiogram Echocardiogram Vital Signs: Blood pressure Pulse	Used to evaluate: Ischemic or congestive hepatic injury	Performed locally. If findings are clinically significant, report as an adverse event.
Urine Chemistry: Drug screen	Used to evaluate: Hepatotoxicity due to cocaine, opiates and other illicit substances	Utilize a Hepatic Monitoring central lab collection kit
Hepatitis D Virus (HDV) Testing: HDV antibody	Used to evaluate/rule out: Acute HDV infection.	Utilize a Hepatic Monitoring central lab collection kit and only select required test needed.
Microbiology: Cultures: Blood Urine	Used to evaluate/rule out: Sepsis or systemic infection	Perform locally. If findings are clinically significant, report as an adverse event.
Slit lamp eye examination (Kayser-Fleisher rings) Genetic evaluation	Used to evaluate/rule out: Wilson's disease	Perform locally. If findings are clinically significant, report as an adverse event.
Other Chemistry: Ceruloplasmin Copper	Used to evaluate/rule out: Wilson's disease	Utilize a Hepatic Monitoring central lab collection kit

*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

Term	Definition
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration versus time curve
AUC(0-∞)	area under the concentration versus time curve from the time of dosing to infinity
CFR	Code of Federal Regulations
CI	confidence interval
C_{max}	maximum observed plasma concentration
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all study-related, good clinical practice (GCP), and applicable regulatory requirements.
CP	clinical pharmacologist
CRF	case report form
CRP	clinical research physician: Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician or other medical officer.
CRU	clinical research unit
CV	coefficient of variation
DDI	drug-drug interaction
ECG	electrocardiogram
enroll	The act of assigning a participant to a treatment. Participants who are enrolled in the study are those who have been assigned to a treatment.
enter	Participants entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.

FDA	Food and Drug Administration
GCP	good clinical practice
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
informed consent	A process by which a participant voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the participant's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
IRB	Institutional Review Board
MTC	medullary thyroid cancer
NSCLC	non-small cell lung cancer
participant	Equivalent to CDISC term "subject": an individual who participates in a clinical trial, either as recipient of an investigational medicinal product or as a control
P-gp	P-glycoprotein
PK	pharmacokinetics
QTc	corrected QT interval
QTcF	QT interval correct for heart rate using Fridericia's formula
RNA	ribonucleic acid
SAE	serious adverse event
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
SoA	Schedule of Activities
$t_{1/2}$	terminal half-life
TBL	total bilirubin

t_{max}	time to maximum observed plasma concentration
ULN	upper limit of normal

10.8. Appendix 8: Protocol Amendment History

Not applicable.

10.9. Appendix 9: 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): 03 March 2021

This amendment is considered to be nonsubstantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment

To include clarification regarding how the percentage of the standardized meal to be consumed by each participant will be calculated.

Section # and Name	Description of Change	Brief Rationale
5 Study Population	Clinical laboratory assessments and vital signs may be repeated at the discretion of the investigator in order to confirm eligibility	per request from the PI
5.1 Inclusion Criteria	Bilateral salpingectomy added to inclusion #6	for consistency across the protocol
5.2 Exclusion Criteria	ECG exclusion now applicable at screening only instead of during 'baseline period'	for clarity
5.3.1 Meals and Dietary Restrictions	Text amended to outline: • that components of the standardized meal will be weighed and documented in grams both pre- and post-meal to determine the percentage of the meal consumed by the participant. • that participants will complete the meal 30 minutes prior to dosing.	for clarity
8.2.3 Electrocardiograms	ECGs will be interpreted by the investigator – not a qualified physician or qualified designee	for clarity

10.2 Appendix 2: Clinical Laboratory Tests	Partial thromboplastin time removed from list of coagulation parameters	vendor does not perform PTT assay; only aPTT
	Table footnote added to state that urinalysis will be performed by dipstick	for clarity
Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information	Tubal ligation added to the category description of women not of childbearing potential	for consistency across the protocol
	Bilateral salpingectomy added to the category description of women not required to use contraception	for consistency across the protocol

11. References

Boehringer Ingelheim. Pradaxa® (dabigatran etexilate) prescribing information. July 2020; Accessed at https://docs.boehringer-ingelheim.com/Prescribing%20Information/PIs/Pradaxa/Pradaxa.pdf on 10 March 2020.

FDA Clinical DDI Draft Guidance: In Vitro Drug Interaction Studies – Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions Guidance for Industry, 2020. Accessed at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/vitro-drug-interaction-studies-cytochrome-p450-enzyme-and-transporter-mediated-drug-interactions on 15 July 2020.

Härtter S, Sennewald R, Nehmiz G, Reilly P. Oral bioavailability of dabigatran etexilate (Pradaxa(®)) after co-medication with verapamil in healthy subjects. *Br J Clin Pharmacol. 2013 Apr; 75(4):1053-62.*

International Transporter Consortium, Giacomini KM, Huang SM, et al. Membrane transporters in drug development. *Nat Rev Drug Discov*. 2010;9(3):215-236.

Levey, Andrew S., Lesley A. Stevens, Christopher H. Schmid, Yaping (Lucy) Zhang, Alejandro F. Castro, Harold I. Feldman, John W. Kusek, et al. 2009. "A New Equation to Estimate Glomerular Filtration Rate." Annals of Internal Medicine 150 (9): 604.

Loxo Oncology, Inc. Selpercatinib (LOXO-292) – Investigator's Brochure (Version 7.0) 01 June 2020.

Stangier J. Clinical pharmacokinetics and pharmacodynamics of the oral direct thrombin inhibitor dabigatran etexilate. *Clin Pharmacokinet*. 2008;47(5):285-295.

Stangier J, Rathgen K, Stähle H, et al. The pharmacokinetics, pharmacodynamics and tolerability of dabigatran etexilate, a new oral direct thrombin inhibitor, in healthy male subjects. *Br J Clin Pharmacol*. 2007 Sep;64(3):292-303.

Leo Document ID = 34785e49-67a1-46f8-8eaa-b18bbd659f33

Approver: [redacted] PPD

Approval Date & Time: 04-Mar-2021 17:26:49 GMT

Signature meaning: Approved

Approver: [redacted] PPD

Approval Date & Time: 05-Mar-2021 14:32:39 GMT

Signature meaning: Approved