Protocol J2G-MC-JZJB(i)

A Multicenter, Randomized, Open-label, Phase 3 Trial Comparing Selpercatinib to Physicians Choice of Cabozantinib or Vandetanib in Patients with Progressive, Advanced, Kinase Inhibitor Naïve, RET-Mutant Medullary Thyroid Cancer (LIBRETTO-531)

NCT04211337

Approval Date: 11-Aug-2023

Title Page

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Protocol Number: J2G-MC-JZJB

Amendment Number: i

Compound Number: LY3527723

Study Phase: Phase 3

Short Title: A Phase 3 Trial Comparing Selpercatinib to Cabozantinib or Vandetanib in Patients with *RET*-Mutant Medullary Thyroid Cancer

Acronym: JZJB

Sponsor Name: Eli Lilly and Company

Legal Registered Address: Indianapolis, Indiana, USA 46285

Regulatory Agency Identifier Number(s)

IND: 144696

EudraCT: 2019-001978-28

EU trial number: 2023-506782-56-00

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

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Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Amendment (h)	*10-May-2023*
Amendment (g)	*28-Oct-2022*
Amendment (f)	*06-Apr-2022*
Amendment (e)	*04-Nov-2021*
Amendment (d)	*15-Feb-2021*
Amendment (c)	*10-Jun-2020*
Amendment (b)	*18-Nov-2019*
Amendment (a)	*12-Nov-2019*
Original Protocol	*30-Jun-2019*

Amendment (i)

This amendment is considered to be substantial.

The amendment is considered to be substantial because it is likely to have a significant impact on the safety or the rights of the study participants

Overall Rationale for the Amendment:

The primary purpose of this amendment is to update as per the latest Investigator Brochure (IB) and to align with EU Clinical Trial Regulation (EU-CTR) requirements.

Section # and Name	Description of Change	Brief Rationale
1.1. Synopsis	Added • Regulatory Agency Identifier Number(s) • Study Population • Ethical Considerations of Benefit/Risk	For EU-CTR compliance
6. Study Intervention	Updated the definition of study intervention	For EU-CTR compliance
6.1.1. Adult Dosing	Added last row for "Authorized as defined by EU Clinical Trial Regulation"	For EU-CTR compliance
6.1.2. Adolescent Dosing	Added last row for "Authorized as defined by EU Clinical Trial Regulation"	For EU-CTR compliance
6.1.4. Packaging and labeling	Added new section	For EU-CTR compliance
6.6.1. Dose Modifications for Selpercatinib Hypersensitivity	Updated the language in second paragraph	Updated as per Selpercatinib IB (Aug 2023)
6.6.5 Dose Modification for Selpercatinib Interstitial Lung Disease or Pneumonitis	Added new section for updated dose modification guidance for Interstitial Lung Disease/Pneumonitis	Updated as per Selpercatinib IB (Aug 2023)
8.2.2.2. Chylothorax and Chylous Ascites Monitoring	Added new section	Updated as per Selpercatinib IB (Aug 2023)

Section # and Name	Description of Change	Brief Rationale
8.2.2.3. Renal Safety Monitoring	Added new section	Updated as per Selpercatinib IB (Aug 2023)
8.2.2.4. Thyroid Function Monitoring	Added new section for hypothyroidism to provide additional guidance	Updated as per Selpercatinib IB (Aug 2023)
8.3 Adverse Events and Serious Adverse Events	Added definition and details for adverse events	For EU-CTR compliance
8.3.3. Regulatory Reporting Requirements for SAEs	Updated the language	For EU-CTR compliance
9.4.1. General Statistical Considerations	Added a paragraph on handling of missing, unused, and spurious data	For EU-CTR compliance
10.1.1. Regulatory and Ethical Considerations	Added a bullet point regarding reporting of significant issues related to participant's safety, rights, and data integrity	For EU-CTR compliance
10.1.3. Data Protection	Updated the required language	For EU-CTR compliance
10.1.5. Dissemination of Clinical Study Data	Added paragraph on "Reports"	For EU-CTR compliance
Throughout the protocol	Minor formatting and editorial changes	Minor, therefore, not detailed

Table of Contents

1. Protocol Summary

1.1. Synopsis

Protocol Title:

A Multicenter, Randomized, Open-label, Phase 3 Trial Comparing Selpercatinib to Physicians Choice of Cabozantinib or Vandetanib in Patients with Progressive, Advanced, Kinase Inhibitor Naïve, *RET*-Mutant Medullary Thyroid Cancer (LIBRETTO-531)

Short Title:

A Phase 3 Trial Comparing Selpercatinib to Cabozantinib or Vandetanib in Patients with Medullary Thyroid Cancer

Regulatory Agency Identifier Number(s)

IND: 144696

EudraCT: 2019-001978-28

EU trial number: 2023-506782-56-00

Rationale:

Medullary thyroid cancer (MTC) accounts for 1% to 2% of thyroid cancers in the United States (SEER 2018). The majority of MTCs are sporadic, with approximately 20% to 25% hereditary due to a germline activating mutation in the *RET* gene. Most sporadic MTCs harbor activating *RET* mutations as well. The clinical course of MTC is highly heterogeneous, varying from indolent tumors that remain unchanged for many years to aggressive cancers associated with high mortality. Although surgery can be curative for the approximately 85% of patients who present with localized disease, approximately 50% develop recurrent disease. Metastatic MTC is incurable. Treatment with the multikinase inhibitors (MKIs) cabozantinib or vandetanib is the standard treatment for patients with symptomatic and/or progressive metastatic MTC. However, the efficacy of these MKIs is ultimately limited by incomplete inhibition of *RET* in tumors in patients, significant toxicity from stronger inhibition of other targets and poor pharmacokinetics (PK). As a result, most patients treated with these agents experience significant toxicities requiring dose interruptions, reductions (35% to 79%), and/or treatment cessation (12% to 16%) (Wells et al. 2012, Elisei et al. 2013).

Selpercatinib is a highly potent and specific small molecule inhibitor of the *RET* kinase, with minimal inhibition of other kinase and non-kinase targets. A Phase 1/2 study (LIBRETTO-001) was designed to assess the safety, PK and anti-tumor activity of selpercatinib in patients with *RET*-altered solid tumors. The Phase 1 portion of the study has been completed and the Phase 2 portion is ongoing. Initial data from Phase 1 was recently presented (Drilon et al. 2018; Oxnard et al. 2018; Wirth et al. 2018). As of 02 April 2018, 82 patients were treated at 8 dose levels (20 mg QD to 240 mg BID). Treatment-emergent adverse events (TEAEs) were monitorable and reversible. A dose of 160 mg BID has been selected for Phase 2.

The investigator-assessed overall response rate (ORR) and confirmed ORR (cORR) by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 in patients with *RET* mutant MTC were 59%

(n = 17/29) and 56% (n = 15/27, respectively, with 94% (n = 16/17) of responses ongoing with a median follow up of 7.6 months (8.4 months for responders).

Given its manageable toxicity profile and evidence of durable antitumor activity in patients with advanced *RET* mutant MTC, selpercatinib may be of benefit in delaying treatment failure and disease progression and improving survival in patients with progressive, advanced MTC who have not previously received cabozantinib or vandetanib.

Objectives and Endpoints

Objectives	Endpoints
Primary	
• To compare PFS of patients with progressive, advanced, kinase inhibitor naïve, *RET*-mutant MTC treated with selpercatinib versus cabozantinib or vandetanib.	• PFS by BICR
Secondary	
• To compare other efficacy outcomes, based on RECIST 1.1 criteria, observed in patients with progressive, advanced, kinase inhibitor naïve, *RET*-mutant MTC treated with selpercatinib versus cabozantinib or vandetanib.	• TFFS by BICR • TFFS by investigator • PFS by investigator • ORR by investigator and BICR • DoR by investigator and BICR • OS • PFS2 by investigator
• To evaluate the safety and tolerability of selpercatinib compared to cabozantinib or vandetanib.	• Safety per CTCAE v5.0 (including but not limited to): incidence and severity of TEAEs, SAEs, deaths, and clinical laboratory abnormalities.
• To compare the tolerability of selpercatinib versus cabozantinib or vandetanib.	• Proportion of time with high-side-effect bother based on FACT-GP5
• To assess/evaluate performance of local *RET* laboratory tests compared to a single, central test.	• *RET* mutation status
• To assess the PK of selpercatinib in patients receiving selpercatinib.	• Predose plasma concentrations at Day 8 of Cycle 1, and at Day 1 of Cycles 2 through 6.

Abbreviations: BICR = blinded independent central review; CTCAE = Common Terminology Criteria for Adverse Events; DoR = duration of response; FACT-GP5 = Functional Assessment of Cancer Therapy-Side Effects; MTC = medullary thyroid cancer; ORR = overall response rate; OS = overall survival; PFS = progression free survival; PFS2 = progression-free survival 2; PK = pharmacokinetics; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; TEAE = treatment-emergent adverse event; TFFS = treatment failure-free survival.

Overall Design:

This is a global, multicenter, randomized (2:1), open-label, Phase 3 study comparing selpercatinib (treatment Arm A) to physician's choice of cabozantinib or vandetanib (treatment Arm B) in patients with progressive, advanced, kinase inhibitor naïve, *RET*-mutant MTC.

Patients will be stratified based on:

- *RET* mutation: M918T vs. other
- Intended treatment if randomized to control arm: cabozantinib vs. vandetanib.

Patients with histologically confirmed, unresectable, locally advanced, or metastatic MTC who have not received previous treatment with a kinase inhibitor are eligible. Patients are required to have radiologic progressive disease per RECIST 1.1 at screening compared with an image obtained within the prior 14 months and to have a documented *RET* mutation in tumor or germline DNA. Both radiographic progression and *RET* mutation must be confirmed by the sponsor prior to patient randomization.

Patients will be randomized in a 2:1 ratio to receive selpercatinib (treatment Arm A) or physician's choice of cabozantinib (treatment Arm B1) or vandetanib (treatment Arm B2). Patients assigned to the control arm cannot switch from cabozantinib to vandetanib or from vandetanib to cabozantinib during the study (under exceptional circumstances, switch from vandetanib to cabozantinib may be allowed as outlined in Section 6.1.3). Treatment will continue until disease progression, unacceptable toxicity, or death.

Patients randomized to Arm B who discontinue treatment and who have radiographic disease progression that is confirmed by blinded independent central review (BICR) may be eligible for crossover to selpercatinib if they meet the eligibility criteria for crossover (see Section 5.2.1).

Disclosure Statement:

This is a randomized, active-treatment study with 2 arms where the participant and investigator will not be blinded, however, to preserve the integrity of the trial, the sponsor will not have unblinded access to aggregate data from the clinical database.

Study Population

- Participants of an acceptable age to provide informed consent according to local regulations and are at least 18 years of age (patients as young as 12 years of age will be allowed if permitted by local regulatory authorities and institutional review boards).
- Histologically or cytologically confirmed, unresectable, locally advanced and/or metastatic MTC and no prior history of treatment with kinase inhibitors for advanced/metastatic disease.
- Radiographic progressive disease per RECIST 1.1 at screening compared with a previous image taken within the prior 14 months as assessed by the BICR. Patients with measurable or non-measurable but evaluable disease are eligible; however, patients with non-measurable disease may not have disease limited to bone sites only.
- A *RET* gene alteration identified in a tumor, germline DNA or blood sample (for example, circulating free DNA [cfDNA]).
- Eastern Cooperative Oncology Group (ECOG) performance status score of 0 to 2.

Number of Participants:

Approximately 250-400 patients will be enrolled to the study.

Intervention Groups and Duration:

	Arm A	Arm B1	Arm B2
Intervention	Selpercatinib	Cabozantinib	Vandetanib
Adult Dose	160 mg BID	140 mg QD	300 mg QD[b]
Adolescent Dose[a] Approximate Adult Equivalent dose	92 mg/m^2 BID 160 mg BID	40 mg/m^2 QD 72 mg QD	See dosing guide
Cycle length is 28 days for all treatment arms.			

Abbreviations: BID = twice daily; QD = once daily

[a] refer to respective nomograms in Section 6.1 for the exact dosing in adolescent patients. A reduced starting dose of vandetanib should be used in adolescent patients with moderate renal impairment as per the dose reduction table in Section 6.6.

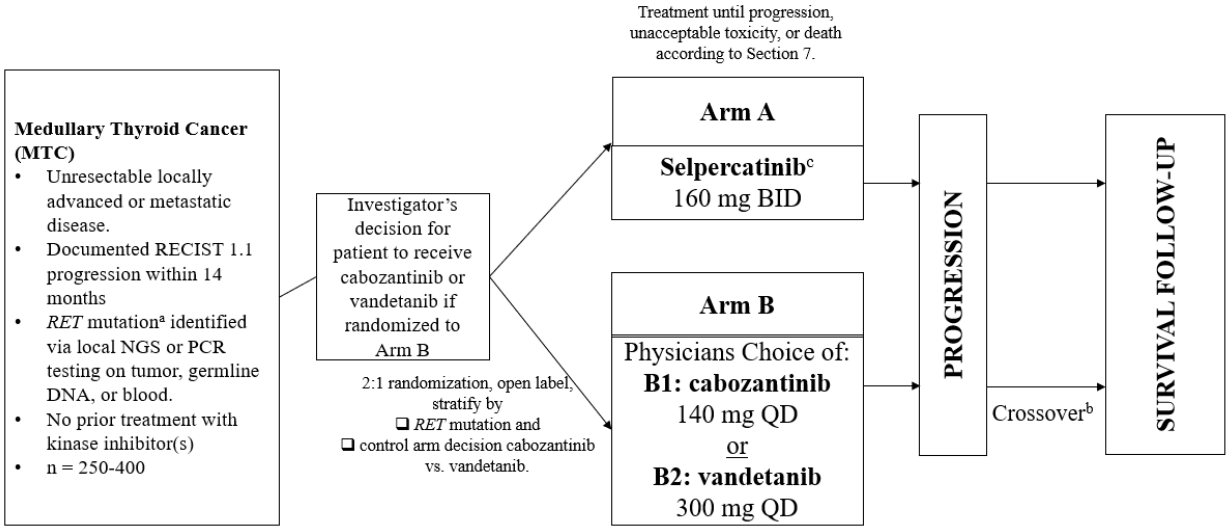
[b] starting dose of vandetanib should be 200 mg in adult patients with moderate renal impairment (creatinine clearance results between 30 and 50 mL/min). In case vandetanib 100-mg tablets are not available, see Section 6.6.

Ethical Considerations of Benefit/Risk:

Based on the manageable toxicity profile and evidence of durable antitumor activity in patients with advanced *RET*-mutant MTC, selpercatinib may be of benefit in delaying treatment failure and disease progression and in improving survival in patients with progressive, advanced MTC who have not previously received cabozantinib or vandetanib. Therefore, the sponsor considers that the benefit/risk balance is positive and supports the proposed Phase 3 Study JZJB, exploring administration of selpercatinib in comparison to cabozantinib or vandetanib in adult and adolescent patients.

Data Monitoring Committee: Yes

1.2. Schema



Abbreviations: BICR = blinded independent central review; BID = twice a day; DNA = deoxyribonucleic acid; MTC = medullary thyroid cancer; NGS = next-generation sequencing; PCR = polymerase chain reaction; QD = once daily; RECIST 1.1= Response Evaluation Criteria in Solid Tumors, version 1.1.

[a] See *RET* activating mutations in MTC (Appendix 6).

[b] To selpercatinib allowed ONLY at radiographic disease progression confirmed by BICR.

[c] Adolescent dose is as follows:

- Selpercatinib: 92 mg/m^2 BID
- Cabozantinib: 40 mg/m^2 QD
- Vandetanib: See dosing guide in Section 6.1.

(Refer to respective nomograms in Section 6.1 for the exact dosing in adolescent patients).

1.3. Schedule of Activities (SoA)

This section includes the following SoAs:

- Pre-screening SoA
- Screening, On-Study, and Post-Study Treatment Follow-Up SoA for Patients on Arm A and Arm B
- Exceptional Control Arm Switch Treatment (for participants switching from vandetanib to cabozantinib)
- Optional Crossover Treatment (for patients crossing over from Arm B to Arm A)
- Continued Access SoA for All Patients

1.3.1. Pre-screening Schedule of Activities

Visit	Prescreening	Instructions
Prescreening ICF for *RET* testing	X	OPTIONAL: In geographies or sites where *RET* testing is not standard of care and/or an acceptable local test (as defined by Sponsor) is not available, a pre-screening consent will be used to provide information to the patient regarding testing to determine tumor *RET* status. If it is considered safe to perform, patients who do not have sufficient available tumor tissue may undergo a fresh tumor biopsy/FNA to determine initial eligibility. If it is unclear that a patient's *RET* result will be considered eligible for enrollment, the *RET* result may be submitted to the Sponsor for review prior to main study consent.
Prescreening ICF for radiologic imaging submission for BICR review	X	OPTIONAL: If the imaging was performed as a part of standard of care, the imaging can be submitted to confirm progression by BICR.
Demographic Information	X	
AE collection	X	See Section 8.3. During Pre-Screening, only AEs reasonably possibly related to study procedures should be recorded in the eCRF.

Abbreviations: AE = adverse event; BICR = blinded independent central review; eCRF = electronic case report form; FNA = fine needle aspirate; ICF = informed consent form.

1.3.2. Screening, On-Study, and Post-Study Treatment Follow-Up Schedule of Activities for Patients on Arm A and Arm B

Screening, On-Study, and Post-Study Treatment Follow-Up Schedule of Activities for Patients on Arm A and Arm B											
	Screening		**On-Treatment**				**Safety assessments prior to crossover**		**Post-Study Treatment**		
			Cycle = 28 days				**(only for patients on**				
							Arm B)				
	(Day Relative to C1D1)		**Cycle 1**			**Cycle 2-n**	**V201[a]**		**Short-term follow-up[a]**	**Long term Follow-up[b]**	**Instructions**
			(±3 days)			(±3 days)	Day 1-30 (±7 days)	1-x days	(30 ± 7 days)	(90 ± 14 days)	
	≤42	**≤7**	**D1**	**D8**	**D15**	**D1**	**N/A**	**N/A**	**V801**	**V802-8XX**	
Procedure											
Molecular Pathology Report(s) describing *RET* alterations (germline or tumor)	X										For all patients, redacted report(s) must be submitted for review. The test may have been performed prior to consent, but sponsor must confirm acceptability of results, preferably prior to other screening procedures.
Informed consent	X										ICF must be signed before any protocol-specific procedures are performed. Any procedures performed as standard of care before consent that fall within the screening window may be used. See Appendix 1.
Demographic Information	X										If this information is collected at the Pre-screening visit, do not collect again at the Screening visit.
Inclusion/ exclusion criteria	X										See Section 5. Must be confirmed before any on treatment procedures are performed.

Screening, On-Study, and Post-Study Treatment Follow-Up Schedule of Activities for Patients on Arm A and Arm B											
	Screening		**On-Treatment**				**Safety assessments prior to crossover**		**Post-Study Treatment**		
			Cycle = 28 days				**(only for patients on**				
							Arm B)				
	(Day Relative to C1D1)		**Cycle 1**			**Cycle 2-n**	**V201[a]**		**Short-term follow-up[a]**	**Long term Follow-up[b]**	**Instructions**
			(±3 days)			(±3 days)	Day 1-30 (±7 days)	1-x days	(30 ± 7 days)	(90 ± 14 days)	
	≤42	**≤7**	**D1**	**D8**	**D15**	**D1**	**N/A**	**N/A**	**V801**	**V802-8XX**	
Procedure											
Medical history	X										Including assessment of pre-existing conditions, historical illnesses, prior anticancer therapy, and habits.
Concomitant medication	X		X				X		X		• At baseline, record prior and concurrent medications. • Record all premedication, supportive care, and concomitant medication continuously at every visit and throughout the study.
Physical examination (≥18 years of age)	X		X	X		See Instructions	X		X		Physical examination and review of relevant systems at Screening. Symptom-directed physical examinations may be performed at other time points. Perform on Day 1 of Cycles 2-16. After completion of 1 year of treatment, obtain every 12 weeks in adult patients (Cycles 16, 19, 22, etc.).
Physical examination (<18 years of age)	X		X	X		X	X		X		Physical examination and review of relevant systems at Screening. Symptom-directed physical examinations may be performed at other time points. Physical exam will be performed on adolescent patients every 4 weeks starting on Day 1 of Cycle 2-n and throughout.

Screening, On-Study, and Post-Study Treatment Follow-Up Schedule of Activities for Patients on Arm A and Arm B											
	Screening		**On-Treatment**				**Safety assessments prior to crossover**		**Post-Study Treatment**		
			Cycle = 28 days				**(only for patients on**				
							Arm B)				
	(Day Relative to C1D1)		**Cycle 1**			**Cycle 2-n**	**V201[a]**		**Short-term follow-up[a]**	**Long term Follow-up[b]**	**Instructions**
			(±3 days)			(±3 days)	Day 1-30 (±7 days)	1-x days	(30 ± 7 days)	(90 ± 14 days)	
	≤42	**≤7**	**D1**	**D8**	**D15**	**D1**	**N/A**	**N/A**	**V801**	**V802-8XX**	
Procedure											
Vital signs (≥18 years of age)	X		X	X		See Instructions	X		X		Measure vital signs: height at baseline only. Perform on Day 1 of Cycles 2-16: weight, systolic and diastolic blood pressure, pulse rate, and body temperature. After completion of 1 year of treatment, obtain every 12 weeks in adult patients (Cycles 16, 19, 22 etc.).
Vital signs (<18 years of age)	X		X	X		X	X		X		Vital signs will be performed on adolescent patients every 4 weeks starting on Day 1 of Cycle 2-n and throughout. Height should be measured every 6 months until they reach the age of 18.
Tanner staging	X					See instructions	X		X		For patients under age 18. Perform every 6 months (±2 weeks); may discontinue when sexual maturity is reached.
AE collection	X		X				X		X		• Collect continuously at every visit and throughout the study • CTCAE Version 5.0 • During the short term follow-up visits, collect all AEs/SAEs. Thereafter, collect only SAEs related to study treatment or protocol procedures • Ongoing drug related AEs at the end of short-term follow-up the patient should be

Screening, On-Study, and Post-Study Treatment Follow-Up Schedule of Activities for Patients on Arm A and Arm B											
	Screening		**On-Treatment**				**Safety assessments prior to crossover**		**Post-Study Treatment**		
			Cycle = 28 days				**(only for patients on**				
							Arm B)				
	(Day Relative to C1D1)		**Cycle 1**			**Cycle 2-n**	**V201[a]**		**Short-term follow-up[a]**	**Long term Follow-up[b]**	**Instructions**
			(±3 days)			(±3 days)	Day 1-30 (±7 days)	1-x days	(30 ± 7 days)	(90 ± 14 days)	
	≤42	**≤7**	**D1**	**D8**	**D15**	**D1**	**N/A**	**N/A**	**V801**	**V802-8XX**	
Procedure											
											followed every 30 days until the event is resolved, the event is no longer considered to be drug related, the event becomes stable or returns to baseline, a new treatment is initiated for the patient, or the patient dies or is lost to follow-up.
ECOG PS (≥18 years of age)	X		X			See Instructions	X		X		During study treatment, perform ≤3 days prior to treatment, perform on Day 1 of Cycles 2-16, then obtain every 12 weeks in adult patients (Cycles 16, 19, 22, etc.).
ECOG PS (<18 years of age)	X		X			X	X		X		During study treatment, perform ≤3 days prior to treatment. ECOG PS will be performed on adolescent patients every 4 weeks starting on Day 1 of Cycle 2-n and throughout.
ECG	X		X	X		See instructions					Obtain triplicate local ECGs at Screening, C1D1, C1D8, and on Day 1 of C2-6. It is preferable to obtain ECGs approximately 2 hours after dosing. Patients receiving vandetanib (Arm B2) continue to have ECGs performed every 3 months post Cycle 6 (consider additional ECG at C16D1 so subsequent ECGs align with onsite clinical visit schedule). See Section 8.2.1.

Screening, On-Study, and Post-Study Treatment Follow-Up Schedule of Activities for Patients on Arm A and Arm B											
	Screening		**On-Treatment**				**Safety assessments prior to crossover**		**Post-Study Treatment**		
			Cycle = 28 days				**(only for patients on**				
							Arm B)				
	(Day Relative to C1D1)		**Cycle 1**			**Cycle 2-n**	**V201[a]**		**Short-term follow-up[a]**	**Long term Follow-up[b]**	**Instructions**
			(±3 days)			(±3 days)	Day 1-30 (±7 days)	1-x days	(30 ± 7 days)	(90 ± 14 days)	
	≤42	**≤7**	**D1**	**D8**	**D15**	**D1**	**N/A**	**N/A**	**V801**	**V802-8XX**	
Procedure											
Hematology (≥18 years of age)	X		X		X	See Instructions	X		X		If screening testing is performed ≤7 days prior to C1D1, repeat testing does not need to occur on C1D1. See Appendix 2. Perform on Day 1 of Cycles 2-16. After completion of 1 year of treatment, obtain every 12 weeks in adult patients (Cycles 16, 19, 22, etc.).
Hematology (<18 years of age)	X		X		X	X	X		X		If screening testing is performed ≤7 days prior to C1D1, repeat testing does not need to occur on C1D1. See Appendix 2. Hematology will be performed on adolescent patients every 4 weeks starting on Day 1 of Cycle 2-n and throughout.
Coagulation	X								X		See Appendix 2. Perform at baseline and as clinically indicated.
Chemistry panel (≥18 years of age)	X		X			See Instructions	X		X		If screening testing is performed ≤7 days prior to C1D1, repeat testing does not need to occur on C1D1. See Appendix 2. Perform on Day 1 of Cycles 2-16. After completion of 1 year of treatment, obtain every 12 weeks in adult patients (Cycles 16, 19, 22, etc.).

Screening, On-Study, and Post-Study Treatment Follow-Up Schedule of Activities for Patients on Arm A and Arm B											
	Screening		**On-Treatment**				**Safety assessments prior to crossover**		**Post-Study Treatment**		
			Cycle = 28 days				**(only for patients on**				
							Arm B)				
	(Day Relative to C1D1)		**Cycle 1**			**Cycle 2-n**	**V201[a]**		**Short-term follow-up[a]**	**Long term Follow-up[b]**	**Instructions**
			(±3 days)			(±3 days)	Day 1-30 (±7 days)	1-x days	(30 ± 7 days)	(90 ± 14 days)	
	≤42	**≤7**	**D1**	**D8**	**D15**	**D1**	**N/A**	**N/A**	**V801**	**V802-8XX**	
Procedure											
Chemistry panel (<18 years of age)	X		X			X	X		X		If screening testing is performed ≤7 days prior to C1D1, repeat testing does not need to occur on C1D1. See Appendix 2. Chemistry panel will be performed on adolescent participants every 4 weeks starting on Day 1 of Cycle 2-n and throughout.
Hepatic monitoring					X	See instructions					See Appendix 2. Should be performed on C1D15, C2D15, and C3D15, then as clinically indicated.
Thyroid panel	X					See instructions					See Appendix 2. Collect at baseline and as clinically indicated.
Pregnancy test		X	X	See Instructions			See Instructions		X		• Applies only to women of childbearing potential. • Note: during study treatment, perform at screening, C1D1 (within 24 hours prior to first dose of study drug), and thereafter as required per local regulations and/or institutional guidelines. • See Appendix 2

Screening, On-Study, and Post-Study Treatment Follow-Up Schedule of Activities for Patients on Arm A and Arm B											
	Screening		**On-Treatment**				**Safety assessments prior to crossover**		**Post-Study Treatment**		
			Cycle = 28 days				**(only for patients on**				
							Arm B)				
	(Day Relative to C1D1)		**Cycle 1**			**Cycle 2-n**	**V201[a]**		**Short-term follow-up[a]**	**Long term Follow-up[b]**	**Instructions**
			(±3 days)			(±3 days)	Day 1-30 (±7 days)	1-x days	(30 ± 7 days)	(90 ± 14 days)	
	≤42	**≤7**	**D1**	**D8**	**D15**	**D1**	**N/A**	**N/A**	**V801**	**V802-8XX**	
Procedure											
Urine Protein (≥18 years of age)				X		See Instructions	X		X		Only for patients receiving cabozantinib. Perform on Day 1 of Cycles 2-16. After completion of 1 year of treatment, obtain every 12 weeks in adult patients (Cycles 16, 19, 22, etc.).
Urine Protein (<18 years of age)				X		X	X		X		Only for patients receiving cabozantinib. Urine protein will be performed on adolescent patients every 4 weeks starting on Day 1 of Cycle 2-n and throughout
Calcitonin, CEA (≥18 years of age)		X			X	See Instructions	X		X		Perform on Day 1 of Cycles 2-16. After completion of 1 year of treatment, obtain every 12 weeks in adult patients (Cycles 16, 19, 22, etc.).
Calcitonin, CEA (<18 years of age)		X			X	X	X		X		Calcitonin, CEA will be performed on adolescent patients every 4 weeks starting on Day 1 of Cycle 2-n and throughout.
Serum Cortisol, ACTH		X			X	See instructions			X		Only in patients with Cushing's disease related to their cancer. Baseline, C1D15, then q 8 weeks (±7 days) for the first 24 weeks after C1D1 and q 12 weeks (±7 days) thereafter (i.e., at the same time as imaging assessments).
Phone visit (collection of						See Instructions					Applicable only for adult patients.

Screening, On-Study, and Post-Study Treatment Follow-Up Schedule of Activities for Patients on Arm A and Arm B											
	Screening		**On-Treatment**				**Safety assessments prior to crossover**		**Post-Study Treatment**		
			Cycle = 28 days				**(only for patients on**				
							Arm B)				
	(Day Relative to C1D1)		**Cycle 1**			**Cycle 2-n**	**V201[a]**		**Short-term follow-up[a]**	**Long term Follow-up[b]**	**Instructions**
			(±3 days)			(±3 days)	Day 1-30 (±7 days)	1-x days	(30 ± 7 days)	(90 ± 14 days)	
	≤42	**≤7**	**D1**	**D8**	**D15**	**D1**	**N/A**	**N/A**	**V801**	**V802-8XX**	
Procedure											
concomitant medications, AEs, labs, and patient dosing diary)											Onsite clinical visit will occur every 28 days from C2 to C16. After C16 the onsite visit will occur every 12 weeks (i.e., C19, C22, C25, etc.). A phone follow-up visit will occur at every non-clinical visit after C16 (i.e., C17, C18, C20, C21, C23, C24, etc.) where details related to concomitant medications, AEs, chemistries, pregnancy test (if required), and patient dosing diary will be captured.
Growth plate imaging	X		See instructions								Only for patients <18 years of age who have not reached full adult height. Knee MRI at baseline and every 6 months ±2 weeks). See Section 8.2.
Radiologic imaging (neck, chest, abdomen, pelvis and other known sites of disease)	X (28 days)		See instructions				See instructions		X		• Perform according to RECIST 1.1 criteria, by the same method used at baseline, q 8 weeks (±7 days) for the first 24 weeks after C1D1 and q 12 weeks (±7 days) thereafter until radiographic disease progression or death, whichever occurs first. • If the imaging submitted to confirm progression by BICR was performed more than 28 days prior to dosing, new imaging should be completed as the pre-dosing

Screening, On-Study, and Post-Study Treatment Follow-Up Schedule of Activities for Patients on Arm A and Arm B											
	Screening		**On-Treatment**				**Safety assessments prior to crossover**		**Post-Study Treatment**		
			Cycle = 28 days				**(only for patients on**				
							Arm B)				
	(Day Relative to C1D1)		**Cycle 1**			**Cycle 2-n**	**V201[a]**		**Short-term follow-up[a]**	**Long term Follow-up[b]**	**Instructions**
			(±3 days)			(±3 days)	Day 1-30 (±7 days)	1-x days	(30 ± 7 days)	(90 ± 14 days)	
	≤42	**≤7**	**D1**	**D8**	**D15**	**D1**	**N/A**	**N/A**	**V801**	**V802-8XX**	
Procedure											
											baseline (but does not need reconfirmed by BICR). • See Section 8.1 for details, including information on suggested modalities.
Submit scans	X		See instructions				X		X		All scans taken for tumor assessment should be submitted to Lilly's designee preferably within 5 business days of collection for central review by the BICR. Repeated submission of scans greater than 10 business days after date of collection will be considered a protocol deviation (unless previously approved by sponsor).
Survival and PFS2 assessment									X	See instructions	Perform q 3 months (±7 days) for the first year off treatment, q 4 months (±14 days) for the second year off treatment, then approximately every 6 months thereafter. Will last until the final analysis for OS. If an in-person visit is not possible, confirm survival by contacting the patient directly via phone. See Section 8.1.1 regarding PFS2 assessment.
Collection of poststudy-treatment									X	X	

Screening, On-Study, and Post-Study Treatment Follow-Up Schedule of Activities for Patients on Arm A and Arm B											
	Screening		**On-Treatment**				**Safety assessments prior to crossover**		**Post-Study Treatment**		
			Cycle = 28 days				**(only for patients on**				
							Arm B)				
	(Day Relative to C1D1)		**Cycle 1**			**Cycle 2-n**	**V201[a]**		**Short-term follow-up[a]**	**Long term Follow-up[b]**	**Instructions**
			(±3 days)			(±3 days)	Day 1-30 (±7 days)	1-x days	(30 ± 7 days)	(90 ± 14 days)	
	≤42	**≤7**	**D1**	**D8**	**D15**	**D1**	**N/A**	**N/A**	**V801**	**V802-8XX**	
Procedure											
anticancer therapy information											
Review patient dosing diary			X	X		See Instructions					Provide patient diary Day 1. Completed daily by patient. Review at each study visit and on phone visits for adult patients from Cycle 16 onward.
Bristol Stool Form Scale and bowel movement frequency			X				X		X		Completed electronically daily by the patient, not site administered except on C1D1 when this should be collected while patient is on site prior to first treatment dose. To be completed through 1 year of treatment then discontinued.
Worst Pain NRS			X				X		X		Completed electronically daily by the patient, not site-administered except on C1D1 when this should be collected while patient is on site prior to first treatment dose. To be completed through 1 year of treatment then discontinued.
Patient-reported AEs (PRO-CTCAE)			X				X		X		Completed electronically by the patient each week, not site-administered except on C1D1 when this should be collected while patient is on site prior to first treatment dose

Screening, On-Study, and Post-Study Treatment Follow-Up Schedule of Activities for Patients on Arm A and Arm B											
	Screening		**On-Treatment**				**Safety assessments prior to crossover**		**Post-Study Treatment**		
			Cycle = 28 days				**(only for patients on**				
							Arm B)				
	(Day Relative to C1D1)		**Cycle 1**			**Cycle 2-n**	**V201[a]**		**Short-term follow-up[a]**	**Long term Follow-up[b]**	**Instructions**
			(±3 days)			(±3 days)	Day 1-30 (±7 days)	1-x days	(30 ± 7 days)	(90 ± 14 days)	
	≤42	**≤7**	**D1**	**D8**	**D15**	**D1**	**N/A**	**N/A**	**V801**	**V802-8XX**	
Procedure											
Patient-reported side-effect burden (FACT-GP5)			X				X		X		Completed electronically by the patient each week, not site-administered except on C1D1 when this should be collected while patient is on site prior to first treatment dose.
Physical function (EORTC IL19)			X				X		X		Completed electronically by the patient each week, not site-administered except on C1D1 when this should be collected while patient is on site prior to first treatment dose.
HRQoL (EORTC QLQ-C30)			X			X	X		X	X	Site-administered at D1 of each cycle using the device provided prior to study intervention, and during follow up at scheduled clinic visits until disease progression. If the patient completed their 30 day assessments (V201) and discontinued prior to crossing over, they will not need to complete the Visit 801 assessments. Starting with C16, obtain every 12 weeks in adult patients (Cycles 16, 19, 22, etc.).

Screening, On-Study, and Post-Study Treatment Follow-Up Schedule of Activities for Patients on Arm A and Arm B											
	Screening		**On-Treatment**				**Safety assessments prior to crossover**		**Post-Study Treatment**		
			Cycle = 28 days				**(only for patients on**				
							Arm B)				
	(Day Relative to C1D1)		**Cycle 1**			**Cycle 2-n**	**V201[a]**		**Short-term follow-up[a]**	**Long term Follow-up[b]**	**Instructions**
			(±3 days)			(±3 days)	Day 1-30 (±7 days)	1-x days	(30 ± 7 days)	(90 ± 14 days)	
	≤42	**≤7**	**D1**	**D8**	**D15**	**D1**	**N/A**	**N/A**	**V801**	**V802-8XX**	
Procedure											
Health Status (EQ-5D-5L)			X			X	X		X	X	Site-administered at D1 of each cycle prior to study intervention using the device provided and during follow up at scheduled clinic visits until disease progression. If the patient completed their 30-day assessments (V201) and discontinued prior to crossing over, they will not need to complete the Visit 801 assessments. Starting with C16, obtain every 12 weeks in adult patients (Cycles 16, 19, 22, etc.).
Blood sample for pharmacokinetics				X		See Instructions					Arm A only: Samples to be drawn pre-dose (-2 to 0 hour) in Cycles 1-6. See Section 8.5.
Whole Blood for genomic DNA (PGx)			X								Sample can be collected at any time if not collected on C1D1.
Archived tumor tissue or fresh biopsy			See Instructions								This sample must be submitted, preferably within 30 days of C1D1. A single sample collected outside of the specific time window will not be considered a protocol deviation. Please submit sample from the most recent biopsy with adequate tissue. See Section 8.8.

Screening, On-Study, and Post-Study Treatment Follow-Up Schedule of Activities for Patients on Arm A and Arm B											
	Screening		**On-Treatment**				**Safety assessments prior to crossover**		**Post-Study Treatment**		
			Cycle = 28 days				**(only for patients on**				
							Arm B)				
	(Day Relative to C1D1)		**Cycle 1**			**Cycle 2-n**	**V201[a]**		**Short-term follow-up[a]**	**Long term Follow-up[b]**	**Instructions**
			(±3 days)			(±3 days)	Day 1-30 (±7 days)	1-x days	(30 ± 7 days)	(90 ± 14 days)	
	≤42	**≤7**	**D1**	**D8**	**D15**	**D1**	**N/A**	**N/A**	**V801**	**V802-8XX**	
Procedure											
Optional post-progression tumor biopsy									See instructions		Can be obtained any time prior to the start of next therapy.
Plasma for cfDNA			X (Pre-dose)		X	See Instructions	X		X		Perform on Day 1 of Cycles 2-16. After completion of 1 year of treatment, obtain every 12 weeks (Cycles 16, 19, 22, etc.). Obtain plasma for cfDNA as soon as its possible after progression or treatment discontinuation.
Administer selpercatinib (Arm A)			See instructions								See Section 6.1.
Administer cabozantinib (Arm B1)			See instructions								See Section 6.1.
Administer vandetanib (Arm B2)			See instructions								See Section 6.1.

Abbreviations: ACTH = adrenocorticotropic hormone; AE = adverse event; BICR = blinded independent review committee; CEA = carcinoembryonic antigen; cfDNA = circulating free deoxyribonucleic acid; CTCAE = Common Terminology Criteria for Adverse Events; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 Version 3.0; EORTC IL19 = European Organisation for Research and Treatment of Cancer Quality of Life questionnaire, item library 19; EQ-5D-5L = 5-level-EuroQol; FACT-GP5 = Functional Assessment of Cancer Therapy-Side Effects; HRQoL = health-related quality of life; ICF = informed consent form; IV = intravenous; MRI = magnetic resonance imaging; NRS = numeric rating scale; PFS = progression-free survival; PRO-CTCAE = patient-reported outcome Common Terminology Criteria for Adverse Events; Q = every; RECIST 1.1 = Response Criteria in Solid Tumors Version 1.1; SAE = serious adverse event.

[a] Short-term follow-up begins when the patient and investigator agree that the patient will no longer continue study treatment and lasts approximately 30 days (±7 days). Please note this is done only for patients not crossing over to selpercatinib after control arm treatment is completed.

All patients in Arm A should complete V801 and will not complete V201.

All patients in Arm B (who are considering crossing over to selpercatinib) will enter Visit 201.

Patients in Arm B that cross over to selpercatinib >37 days (30 days ±7 days) after the last dose of study treatment should complete V201 assessments. If a patient in V201 that has completed the V201 assessments does not enter crossover (V300) they do not need to complete the V801 assessments, but will need to complete V802 assessments.

Patients in Arm B that cross over to selpercatinib in less than 37 days should discontinue from V201 when the decision to be screened for crossover is made. They will not complete the V201 assessments, but rather enter visit 300 and complete the screening assessments for crossover.

Patients in Arm B that will not crossover to selpercatinib should not enter V201. They will not complete the V201 assessment, but rather subsequently enter V801 and complete the V801 assessments

[b] Long-term follow-up begins when the patient completes the 30-day (±7 days) follow-up visit and ends with the patient's death, upon loss to follow-up, or upon overall study completion, whichever is earlier. No follow-up procedures will be performed for a patient who withdraws informed consent unless he or she has explicitly provided permission and consent.

Note: Baseline/screening assessments and laboratory values drawn within the indicated window of C1D1 may be used for both screening/baseline and C1D1 assessments. There is not a defined interval required from randomization to C1D1.

1.3.3. Exceptional Control Arm Switch Treatment (for participants switching from vandetanib to cabozantinib)

This SoA table reflects the additional or revised procedures for control arm switch. Refer to the SoA table, Section 1.3.2 for complete schedule.

Exceptional[a] Control Arm Switch Treatment (for participants switching from vandetanib to cabozantinib)

	Switch Screening	On-Treatment				
		Cycle = 28 days				
	Days relative to start of switch treatment	Cycle X+1			Cycle X+2 – 3	Instructions
		(±3 days)			(±3 days)	
	≤42	D1	D8	D15	D1	
Procedure						
Eligibility criteria for control arm switch	X					See Section 6.1.3.1. Must be confirmed before any switch phase procedures are performed.
Informed consent form	X					ICF must be signed before any switch phase procedures are performed.
Vital signs (≥18 years of age)	X	X	X		See Instructions	Measure vital signs: Perform on Day 1 of Cycles X+2 - X+3: weight, systolic and diastolic blood pressure, pulse rate, and body temperature. After the first 3 cycles of switch treatment, go back to previous frequency, i.e., completion of 1 year of study treatment, obtain every 12 weeks in adult participants only.
Vital signs (<18 years of age)	X	X	X		See instructions	Vital signs will be performed on adolescent participants every 4 weeks starting on Day 1 of Cycle X+2-n and throughout. Height should be measured every 6 months.
ECG	X	X	X		See Instructions	Obtain triplicate local ECGs at screening, on D1 and D8 of Cycle X+1, on Day 1 of Cycles X+2 - X+3. After 3 cycles of switch treatment, go back to previous frequency. It is preferable to obtain ECGs approximately 2 hours after dosing. See Section 8.2.1.

Exceptional[a] Control Arm Switch Treatment (for participants switching from vandetanib to cabozantinib)

	Switch Screening	On-Treatment				
		Cycle = 28 days				
	Days relative to start of switch treatment	Cycle X+1			Cycle X+2 – 3	Instructions
		(±3 days)			(±3 days)	
	≤42	D1	D8	D15	D1	
Procedure						
Hematology (≥18 years of age)	X	X		X	See Instructions	If testing is performed ≤7 days prior to D1 of Cycle X+1, repeat testing does not need to occur on D1 of Cycle X+1. See Appendix 2. Perform on Day 1 of Cycles X+2 - X+3. After completion of 1 year of study treatment, obtain every 12 weeks in adult participants (e.g., Cycles X+16, X+19, X+22, etc.).
Hematology (<18 years of age)	X	X		X	X	If testing at switch screening is performed ≤7 days prior to D1 of Cycle X+1, repeat testing does not need to occur on D1 of Cycle X+1. See Appendix 2. Hematology will be performed on adolescent participants every 4 weeks starting on Day 1 of Cycle X+2 - X+3, and after, go back to previous frequency.
Coagulation	X					See Appendix 2. Perform at switch screening, and as clinically indicated.
Chemistry panel (≥18 years of age)	X	X			See Instructions	If testing at switch screening is performed ≤7 days prior to D1 of Cycle X+1, repeat testing does not need to occur on D1 of Cycle X+1. See Appendix 2. Perform on Day 1 of Cycles X+2 - X+3. After completion of 1 year of study treatment, obtain every 12 weeks in adult participants.
Chemistry panel (<18 years of age)	X	X			X	If testing at switch screening is performed ≤7 days prior to D1 of Cycle X+1, repeat testing does not need to occur on D1 of Cycle X+1. See Appendix 2. Chemistry panel will be performed on adolescent participants every 4 weeks starting on Day 1 of

Exceptional[a] Control Arm Switch Treatment (for participants switching from vandetanib to cabozantinib)

	Switch Screening	On-Treatment				
		Cycle = 28 days				
	Days relative to start of switch treatment	Cycle X+1			Cycle X+2 – 3	Instructions
		(±3 days)			(±3 days)	
	≤42	D1	D8	D15	D1	
Procedure						
						Cycle X+2 - 3 and after 3 first switch cycles, go back to previous frequency.
Hepatic monitoring				X	See Instructions	See Appendix 2. Should be performed at switch screening, on D15 of Cycles X+1, X+2, and X+3, then as clinically indicated.
Thyroid panel	X				See Instructions	See Appendix 2. Collect at switch screening and as clinically indicated.
Pregnancy test	X	X	See instructions			• Applies only to women of childbearing potential. • Note: during switch treatment, perform at switch screening, on D1 of Cycle X+1 (within 24 hours prior to dose) and thereafter as required per local regulations and/or institutional guidelines. • See Appendix 2.
Urine protein (≥18 years of age)			X		See Instructions	Perform on Day 1 of Cycles X+2 - X+n. After completion of 1 year of study treatment, obtain every 12 weeks in adult participants (Cycles X+16, X+19, X+22, etc.).
Urine protein (<18 years of age)			X		X	Urine protein will be performed on adolescent participants every 4 weeks starting on Day 1 of Cycle X+2 - n and throughout.

Exceptional[a] Control Arm Switch Treatment (for participants switching from vandetanib to cabozantinib)						
	Switch Screening	**On-Treatment**				
		Cycle = 28 days				
	Days relative to start of switch treatment	**Cycle X+1**			**Cycle X+2 – 3**	**Instructions**
		(±3 days)			(±3 days)	
	≤42	**D1**	**D8**	**D15**	**D1**	
Procedure						
Radiologic imaging (neck, chest, abdomen, pelvis, and other known sites of disease)	X	See instructions				• Perform according to RECIST 1.1 criteria, by the same method used at baseline, q 8 weeks (±7 days) for the first 24 weeks after C1D1 and q 12 weeks (±7 days) thereafter until radiographic disease progression or death, whichever occurs first. • Perform as scheduled, even if study treatment is omitted. • Perform scans at switch screening if last scan on vandetanib is more than 8 weeks prior to D1 of Cycle X+1. • Brain or bone imaging required only for participants with known or suspected disease at those sites. See Section 8.1.
Submit scans	X	See instructions				All scans taken for tumor assessment should be submitted to Lilly's designee in a timely manner.
Administer cabozantinib		See instructions				See Section 6.1.

Abbreviations: ECG = electrocardiogram; ICF = informed consent form; RECIST 1.1 = Response Criteria in Solid Tumors Version 1.1.

[a] Cycle X refers to the last cycle of control arm treatment before the switch.

1.3.4. Optional Crossover Treatment (for patients crossing over from Arm B to Arm A)

Only applicable for patients initially randomized Arm B (cabozantinib or vandetanib) who have progression that is confirmed by the BICR and who are eligible for crossover treatment.

Optional Crossover Treatment (for patients crossing over from Arm B to Arm A)								
	Crossover Screening	**On-Treatment**				**Post-Study Treatment**		
		Cycle = 28 days						
	Visit 300 (Day relative to start of treatment)	**Visit 301**			**Visit 302-n**	**Short-term follow-up[a]**	**Long term Follow-up[b]**	**Instructions**
		Cycle 1			**Cycle 2-n**			
		(±3 days)			(±3 days)	(30 ± 7 days)	(90 ± 14 days)	
	≤42	**D1**	**D8**	**D15**	**D1**	**V801**	**V802-8XX**	
Procedure								
Inclusion/exclusion criteria for crossover phase	X							See Section 5.2.1. Must be confirmed before any crossover phase procedures are performed
Informed consent form	X							ICF must be signed before any crossover phase procedures are performed. Any procedures performed as standard of care before consent that fall within the screening window may be used.
Concomitant medication	X	X				X		• At baseline, record prior and concurrent medications. • Record all premedication, supportive care, and concomitant medication continuously at every visit and throughout the study.
Physical examination (≥18 years of age)	X	X	X		See Instructions	X		Physical examination and review of relevant systems at Screening. Symptom-directed physical examinations may be performed at other time points. Perform on Day 1 of Cycles 2-16. After completion of 1 year on crossover treatment, obtain every 12 weeks in adult patients (Cycles 16, 19, 22, etc.).
Physical examination (<18 years of age)	X	X	X		X	X		Physical examination will be performed on adolescent patients every 4 weeks starting on Day 1 of Cycle 2-n and throughout.

Optional Crossover Treatment (for patients crossing over from Arm B to Arm A)								
	Crossover Screening	**On-Treatment**				**Post-Study Treatment**		
		Cycle = 28 days						
	Visit 300 (Day relative to start of treatment)	**Visit 301**			**Visit 302-n**	**Short-term follow-up[a]**	**Long term Follow-up[b]**	**Instructions**
		Cycle 1			**Cycle 2-n**			
		(±3 days)			(±3 days)	(30 ± 7 days)	(90 ± 14 days)	
	≤42	**D1**	**D8**	**D15**	**D1**	**V801**	**V802-8XX**	
Procedure								
Vital signs (≥18 years of age)	X	X	X		See Instructions	X		Measure vital signs: height (at baseline only). Perform on Day 1 of Cycles 2-16: weight, systolic and diastolic blood pressure, pulse rate, and body temperature. After completion of 1 year of crossover treatment, obtain every 12 weeks in adult patients (Cycles 16, 19, 22, etc.) only.
Vital signs (<18 years of age)	X	X	X		X	X		Vital signs will be performed on adolescent patients every 4 weeks starting on Day 1 of Cycle 2-n and throughout. Height should be obtained every 6 months until the age of 18.
Tanner Staging	X				See Instructions	X		For patients under age 18. Perform every 6 months (±2 weeks); may discontinue when sexual maturity is reached.
AE collection	X	X				X	X	• Collect continuously at every visit and throughout the study • CTCAE Version 5.0 • During the short term follow-up visits, collect all AEs/SAEs. Thereafter, collect only SAEs related to study treatment or protocol procedures
ECOG PS (≥18 years of age)	X	X			See Instructions	X		During study treatment, perform ≤3 days prior to treatment. Perform on Day 1 of Cycles 2-16. After completion of 1 year of crossover treatment, obtain every 12 weeks in adult patients (Cycles 16, 19, 22, etc.).
ECOG PS (<18 years of age)	X	X			X	X		ECOG PS will be performed on adolescent patients every 4 weeks starting on Day 1 of Cycle 2-n and throughout.
ECG	X	X	X		See Instructions			Obtain triplicate local ECGs at screening, C1D1, C1D8, on Day 1 of C2-6. It is preferable to obtain ECGs approximately 2 hours after dosing. See Section 8.2.1.

Optional Crossover Treatment (for patients crossing over from Arm B to Arm A)								
	Crossover Screening	**On-Treatment**				**Post-Study Treatment**		
		Cycle = 28 days						
	Visit 300 (Day relative to start of treatment)	**Visit 301**			**Visit 302-n**	**Short-term follow-up[a]**	**Long term Follow-up[b]**	**Instructions**
		Cycle 1			**Cycle 2-n**			
		(±3 days)			(±3 days)	(30 ± 7 days)	(90 ± 14 days)	
	≤42	**D1**	**D8**	**D15**	**D1**	**V801**	**V802-8XX**	
Procedure								
Hematology (≥18 years of age)	X	X		X	See Instructions	X		If testing is performed ≤7 days prior to C1D1, repeat testing does not need to occur on C1D1. See Appendix 2. Perform on Day 1 of Cycles 2-16. After completion of 1 year of crossover treatment, obtain every 12 weeks in adult patients (Cycles 16, 19, 22, etc.).
Hematology (<18 years of age)	X	X		X	X	X		If testing is performed ≤7 days prior to C1D1, repeat testing does not need to occur on C1D1. See Appendix 2. Hematology will be performed on adolescent patients every 4 weeks starting Cycle 2-n and throughout.
Coagulation	X					X		See Appendix 2. Perform at crossover screening, V801, and as clinically indicated.
Chemistry panel (≥18 years of age)	X	X			See Instructions	X		If testing is performed ≤7 days prior to C1D1, repeat testing does not need to occur on C1D1. See Appendix 2. Perform on Day 1 of Cycles 2-16. After completion of 1 year of crossover treatment, obtain every 12 weeks in adult patients (Cycles 16, 19, 22, etc.).
Chemistry panel (<18 years of age)	X	X			X	X		If testing is performed ≤7 days prior to C1D1, repeat testing does not need to occur on C1D1. See Appendix 2. Chemistry panel will be performed on adolescent patients every 4 weeks starting Cycle 2-n and throughout.
Hepatic monitoring				X	See Instructions			See Appendix 2. Should be performed on C1D15, C2D15, and C3D15, then as clinically indicated.
Thyroid panel	X				See Instructions			See Appendix 2. Collect at crossover baseline and as clinically indicated.

Optional Crossover Treatment (for patients crossing over from Arm B to Arm A)								
	Crossover Screening	**On-Treatment**				**Post-Study Treatment**		
		Cycle = 28 days						
	Visit 300 (Day relative to start of treatment)	**Visit 301**			**Visit 302-n**	**Short-term follow-up[a]**	**Long term Follow-up[b]**	**Instructions**
		Cycle 1			**Cycle 2-n**			
		(±3 days)			(±3 days)	(30 ± 7 days)	(90 ± 14 days)	
	≤42	**D1**	**D8**	**D15**	**D1**	**V801**	**V802-8XX**	
Procedure								
Pregnancy test	X	X	See instructions			X		• Applies only to women of childbearing potential. • Note: during study treatment, perform C1D1 (within 24 hours prior to dose) and thereafter as required per local regulations and/or institutional guidelines. • See Appendix 2.
Calcitonin, CEA (≥18 years of age)	X			X	See Instructions	X		Perform on Day 1 of Cycles 2-16. After completion of 1 year of crossover treatment, obtain every 12 weeks in adult patients (Cycles 16, 19, 22, etc.).
Calcitonin, CEA (<18 years of age)	X			X	X	X		Calcitonin, CEA will be performed on adolescent patients every 4 weeks starting on Day 1 of Cycle 2-n and throughout.
Serum Cortisol and ACTH	X			X	See Instructions	X		Only for patients with Cushing's disease related to their cancer. Collect at crossover screening, C1D15, then q 8 weeks (±7 days) for the first 24 weeks after C1D1 and q 12 weeks (±7 days) thereafter (i.e., at the same time as imaging assessments).
Phone visit (collection of concomitant medications, AEs, labs, and patient dosing diary)					See Instructions			Applicable only for adult patients. Onsite clinical visit will occur every 28 days from C2 to C16. After C16 the onsite visit will occur every 12 weeks (i.e., C19, C22, C25, etc.). A phone follow-up visit will occur at every non-clinical visit after C16 (i.e.: C17, C18, C20, C21, C23, C24, etc.) where details related to concomitant medications, AEs, chemistries, pregnancy test (if required), and patient dosing diary will be captured.
Growth plate imaging		See instructions						Only for patients <18 years of age who have not reached full adult height. Knee MRI at baseline and every 6 months (±2 weeks). See Section 8.2.

Optional Crossover Treatment (for patients crossing over from Arm B to Arm A)								
	Crossover Screening	**On-Treatment**				**Post-Study Treatment**		
		Cycle = 28 days						
	Visit 300 (Day relative to start of treatment)	**Visit 301**			**Visit 302-n**	**Short-term follow-up[a]**	**Long term Follow-up[b]**	**Instructions**
		Cycle 1			**Cycle 2-n**			
		(±3 days)			(±3 days)	(30 ± 7 days)	(90 ± 14 days)	
	≤42	**D1**	**D8**	**D15**	**D1**	**V801**	**V802-8XX**	
Procedure								
Radiologic imaging (neck, chest, abdomen, pelvis and other known sites of disease)	X	See instructions				X		• Perform according to RECIST 1.1 criteria, by the same method used at baseline, q 8 weeks (±7 days) for the first 24 weeks after C1D1 (V301) and q 12 weeks (±7 days) thereafter until radiographic disease progression or death, whichever occurs first. • Perform as scheduled, even if study treatment is omitted. • Brain/bone imaging required only for patients with known/ suspected disease at those sites. See Section 8.1.
Submit scans	X	See instructions				X		All scans taken for tumor assessment should be submitted to Lilly's designee in a timely manner.
Survival assessment						X	See instructions	Perform q 3 months (±7 days) for the first year off treatment, q 4 months (±14 days) for the second year off treatment, then approximately every 6 months thereafter. If an in-person visit is not possible, confirm survival by contacting the patient directly via phone.
Collection of poststudy-treatment anticancer therapy information						X	X	
Review patient dosing diary		X	X		X			Provide patient diary Day 1. Completed daily by patient. Review at each study visit and on phone visits for adult patients from Cycle 16 onward.
Bristol Stool Form Scale and bowel movement frequency		X				X		Completed electronically daily by the patient, not site administered, except on C1D1 when this should be collected while patient is on site prior to first treatment dose. To be completed through 1 year of study treatment then discontinued.

Optional Crossover Treatment (for patients crossing over from Arm B to Arm A)								
	Crossover Screening	**On-Treatment** Cycle = 28 days				**Post-Study Treatment**		
	Visit 300 (Day relative to start of treatment)	**Visit 301** Cycle 1			**Visit 302-n** Cycle 2-n	**Short-term follow-up[a]**	**Long term Follow-up[b]**	**Instructions**
		(±3 days)			(±3 days)	(30 ± 7 days)	(90 ± 14 days)	
	≤42	**D1**	**D8**	**D15**	**D1**	**V801**	**V802-8XX**	
Procedure								
Worst Pain NRS		X				X		Completed electronically daily by the patient, not site-administered, except on C1D1 when this should be collected while patient is on site prior to first treatment dose. To be completed through 1 year of study treatment then discontinued.
Patient-reported AEs (PRO-CTCAE)		X	X	X	X	X		Completed electronically weekly by the patient, not site-administered, except on C1D1 when this should be collected while patient is on site prior to first treatment dose.
Patient-reported side-effect burden (FACT-GP5)		X	X	X	X	X		Completed electronically weekly by the patient, not site-administered, except on C1D1 when this should be collected while patient is on site prior to first treatment dose.
Physical function (EORTC IL19)		X	X	X	X	X		Completed electronically weekly by the patient, not site-administered, except on C1D1 when this should be collected while patient is on site prior to first treatment dose.
HRQoL (EORTC QLQ-C30)		X			See Instructions	X	X	Site-administered at D1 of each cycle using the device provided, and during follow up at scheduled clinic visits until disease progression. Please collect at C1-n, D1 prior to study intervention. Starting with C16, obtain every 12 weeks in adult patients (Cycles 16, 19, 22, etc.).
Health Status (EQ-5D-5L)		X			See Instructions	X	X	Site-administered at D1 of each cycle using the device provided and during follow up at scheduled clinic visits until disease progression. Please collect at C1-n, D1 prior to study intervention. Starting with C16, obtain every 12 weeks in adult patients (Cycles 16, 19, 22, etc.).
Blood sample for pharmacokinetics			X		X			Samples to be drawn pre-dose (-2 to 0 hour) in Cycles 1-6. See Section 8.5.

Optional Crossover Treatment (for patients crossing over from Arm B to Arm A)								
	Crossover Screening	**On-Treatment**				**Post-Study Treatment**		
		Cycle = 28 days						
	Visit 300 (Day relative to start of treatment)	**Visit 301**			**Visit 302-n**	**Short-term follow-up[a]**	**Long term Follow-up[b]**	**Instructions**
		Cycle 1			**Cycle 2-n**			
		(±3 days)			(±3 days)	(30 ± 7 days)	(90 ± 14 days)	
	≤42	**D1**	**D8**	**D15**	**D1**	**V801**	**V802-8XX**	
Procedure								
Optional post-progression tumor biopsy						See Instructions		Can be obtained any time prior to the start of next therapy
Plasma for cfDNA		X Pre-dose		X	See Instructions	X		Perform on Day 1 of Cycles 2-16. After completion of 1 year of treatment, obtain every 12 weeks (Cycles 16, 19, 22, etc.). Obtain plasma for cfDNA as soon as its possible after progression or treatment discontinuation.
Administer selpercatinib		See instructions						See Section 6.1.

Abbreviations: ACTH = adrenocorticotropic hormone; AE = adverse event; CEA = carcinoembryonic antigen; cfDNA = circulating free deoxyribonucleic acid; CTCAE = Common Terminology Criteria for Adverse Events; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 Version 3.0; EORTC IL19 = European Organisation for Research and Treatment of Cancer Quality of Life questionnaire, item library 19; EQ-5D-5L = 5-level-EuroQol; FACT-GP5 = Functional Assessment of Cancer Therapy-Side Effects; HRQoL = health-related quality of life; ICF = informed consent form; MRI = magnetic resonance imaging; NRS = numeric rating scale; PFS = progression-free survival; PRO-CTCAE = patient-reported outcome Common Terminology Criteria for Adverse Events; Q = every; RECIST 1.1 = Response Criteria in Solid Tumors Version 1.1; SAE = serious adverse event.

[a] Short-term follow-up begins when the patient and investigator agree that the patient will discontinue study treatment.

[b] Long-term follow-up begins when the patient completes the 30-day (±7 days) follow-up visit and ends with the patient's death, upon loss to follow-up, or upon overall study completion, whichever is earlier. No follow-up procedures will be performed for a patient who withdraws informed consent unless he or she has explicitly provided permission and consent.

Note: Crossover baseline/screening assessments and laboratory values drawn within the indicated window of C301D1 may be used for both crossover screening/baseline and C301D1 assessments.

1.3.5. Continued Access Schedule of Activities for all patients

Continued Access Schedule of Activities for all patients			
	Study Treatment	**30-day Follow-Up[a]**	
Visit	**501-5XX**	**901**	
Procedure[b]			**Instructions**
AE collection	X	X	As part of AE collection, monitor vital signs and perform standard laboratory tests (hematology, chemistry, urinalysis, and pregnancy testing) at a minimum frequency of every 12 weeks. All laboratory tests during the continued access period will be performed in local laboratories only.
Administer selpercatinib (Arm A)	X		See Section 6.1.
Administer cabozantinib (Arm B1)	X		See Section 6.1.
Administer vandetanib (Arm B2)	X		See Section 6.1.

Abbreviations: AE = adverse event.

[a] Continued access follow-up begins when the patient and the investigator agree that the patient will no longer continue treatment in the continued access period and lasts approximately 30 days. No follow-up procedures will be performed for a patient who withdraws informed consent unless he or she has explicitly provided permission and consent to allow for follow-up. If it is deemed to be in the best interest of the patient to start a new anticancer treatment prior to the scheduled end of the follow-up visits, the visit duration may be shortened. In this case, the follow-up assessments should be completed prior to the initiation of the new therapy.

[b] Efficacy assessments will be done at the investigator's discretion based on the standard of care.

2. Introduction

2.1. Study Rationale

Selpercatinib is a highly potent and specific inhibitor of the *RET* RTK, with minimal inhibition of other kinase and non-kinase targets, and therefore may be of benefit to patients with MTC that harbor *RET* alterations and/or depend on *RET* activation. This Phase 3 study is intended to confirm the benefit from selpercatinib seen in patients with advanced/metastatic MTC in the LIBRETTO-001 trial and to better understand this benefit in the context of other available treatments for advanced/metastatic MTC.

2.2. Background

RET is a receptor tyrosine kinase (RTK) with critical roles in normal organogenesis and in the maintenance of several adult tissue types, including neural, neuroendocrine, hematopoietic, and male germ cell (Mulligan 2014). Genetic alterations in the *RET* gene are implicated in the pathogenesis of several human cancers. *RET* can be oncogenically activated by 2 primary mechanisms:

(1) chromosomal rearrangements, producing cytoplasmically localized oncogenic hybrid proteins that fuse the *RET* kinase domain with a partner protein dimerization domain (e.g., CCDC6/PTC1, KIF5B, NCOA4/PTC3), thus endowing the kinase with ligand-independent, constitutive activity; and
(2) point mutations that directly or indirectly activate the kinase.

The oncogenic potential of *RET* was first identified as a result of its ability to transform NIH 3T3 cells through deoxyribonucleic acid (DNA) rearrangement (Takahashi et al. 1985). Since its oncogenic potential was first discovered, the identification of additional, activating *RET* gene alterations in several different tumor types clearly implicates *RET* in the pathogenesis of human cancers. *RET* gene fusions have been identified in approximately 6% of sporadic papillary thyroid cancers (PTCs) (Fusco et al. 1987, Cancer Genome Atlas Research 2014) and at even higher frequency in radiation-induced PTCs (Ito et al. 1994, Fugazzola et al. 1995, Bounacer et al. 1997, Nikiforov et al. 1997). In patients with PTC, *RET* gene fusions are associated with adverse prognostic features (Prasad et al. 2016, Su et al. 2016). In addition, activating *RET* gene mutations occur at high frequency in human MTC (>90% hereditary, approximately 50% to 60% sporadic) (Donis Keller et al. 1993, Mulligan et al. 1993, Carlson et al. 1994, Eng et al. 1994, Hofstra et al. 1994, Agrawal et al. 2013, Ji et al. 2015).

In addition to direct, mutation-mediated activation of *RET*, increased *RET* expression in the absence of *RET* mutation may contribute to the growth and survival of some human cancers. For example, *RET* has been shown to be a direct transcriptional target of the estrogen receptor (ER) (Boulay et al. 2008, Wang et al. 2012), a finding that is consistent with:

1. possible ER-mediated increased *RET* expression in tumors from rare families with MTC (Smith et al. 2016);
2. increased *RET* expression in some ER-positive breast cancers that have acquired resistance to anti estrogens (Plaza-Menacho et al. 2010, Spanheimer et al. 2014); and
3. re-sensitization to anti-estrogen treatment through *RET* inhibition (Plaza-Menacho et al. 2010, Morandi et al. 2013, Spanheimer et al. 2014).

Finally, a recent study identified *RET* as a strong negative regulator of Major Histocompatibility Complex class I (MHC-I) expression in several human cancer cell lines of diverse histologies (Brea et al. 2016). This finding suggests a possible role for *RET* inhibition in upregulating the anti-cancer immune response.

Medullary thyroid cancer accounts for 1% to 2% of thyroid cancers in the United States, with approximately 1000 new cases per year (SEER 2018). The majority of MTCs are sporadic, with approximately 20% to 25% hereditary due to a germline activating mutation in the *RET* gene. Most sporadic MTCs harbor activating *RET* mutations as well. National Comprehensive Cancer Network (NCCN) guidelines thus recommend germline *RET* testing for all patients diagnosed with MTC. The clinical course of MTC is highly heterogeneous, varying from indolent tumors that remain unchanged for many years to aggressive cancers associated with high mortality. Although surgery can be curative for the approximately 85% of patients who present with localized disease, approximately 50% develop recurrent disease, indicated by a rising level of serum tumor markers calcitonin (Ct) and/or carcinoembryonic antigen (CEA), which can predate the development of radiographically measurable metastases. Locally recurrent disease is treated with reoperation and/or external beam radiation therapy; however, these treatments are associated with significant morbidity and are often not curative. Metastatic MTC is incurable. Two MKIs, cabozantinib and vandetanib, have received regulatory approval for advanced MTC (irrespective of the presence or absence of a *RET* mutation), with tumor response rates of 28% and 45% and progression-free survival (PFS) improvements (over placebo) of 7.2 and 11.2 months, respectively (Wells et al. 2012, Elisei et al. 2013). However, the efficacy of these MKIs is ultimately limited by incomplete inhibition of *RET* in tumors in patients, significant toxicity from stronger inhibition of other targets (e.g., KDR/VEGFR2, EGFR, MET), and poor PK (i.e., significant drug accumulation and long half-life contributing to toxicity but not efficacy). As a result, most patients treated with these agents experience significant toxicities requiring dose interruptions, reductions (35% with vandetanib, 79% with cabozantinib), and/or treatment cessation (12% with vandetanib, 16% with cabozantinib). There are no approved systemic therapies with proven efficacy after failure of 1 prior MKI.

Adolescent medullary thyroid cancer is rare, making up about 5% of adolescent thyroid cancer (Gerber et al 2015, Hogan et al 2009). Hereditary MTC syndromes are present in almost all children and young adults diagnosed with MTC and are known to be caused by missense mutation in the *RET* proto-oncogene. Treatment options are limited and identical to those of adults. Although the data are limited in adolescent patients with *RET* alterations, vandetanib and cabozantinib have emerged as the standard of care for adolescent patients with *RET* alterations.

In Phase 1 evaluations objective responses with an acceptable safety profile have been reported for both agents (Chuk et al, 2018 and Fox et al 2013).

The combination of high frequency alterations in a less-prevalent cancer like MTC indicates that a significant number of patients with advanced, *RET* mutant MTC could benefit from potent and selective *RET* kinase inhibition.

The different degree of benefit observed in each study was most likely due to the eligibility requirement for recent tumor progression in the cabozantinib study but not the vandetanib study. In subset analyses of both studies, patients whose tumors harbored *RET* activating mutations derived greater benefit than *RET* mutation–negative patients (Wells et al. 2012, Sherman et al. 2016). Preliminary data suggests similar, moderate activity for MKIs with anti-*RET* activity in *RET* fusion positive lung cancer, with response rates of 16% to 53% (depending on the specific MKI and patient population), but PFS of only 3.6 to 7.3 months, in several ongoing Phase 2 studies (Drilon et al. 2016, Lee et al. 2016, Velcheti et al. 2016, Yoh et al. 2016).

Patients with *RET* mutant MTC comprise a population with high unmet need. Chemotherapy is ineffective for MTC; therefore, there is an urgent need to identify new targeted therapies that potently inhibit *RET* in tumors, while sparing other kinase and non-kinase off-targets that contribute to significant toxicity.

2.2.1. Selpercatinib

Selpercatinib is a small molecule designed to block the adenosine triphosphate (ATP) binding site of the *RET* RTK; there is no evidence of covalent or irreversible binding. Selpercatinib causes dose-dependent inhibition of tumor growth in multiple, biologically relevant *RET*-dependent tumor models in vitro and in vivo, including non-small cell lung cancer (NSCLC), MTC, and colorectal cancer cells and tumors harboring KIF5B-*RET* and non-KIF5B-*RET* fusions, with and without the *RET* V804M gatekeeper mutation and activating *RET* mutations found in MTC.

Selpercatinib was selective for 98% of 329 non-*RET* kinases tested in a large in vitro screen. This high degree of selectivity was maintained in additional enzyme and cell-based assays. Selpercatinib at clinically and toxicologically relevant concentrations had no significant effects on a range of other targets and receptors.

Selpercatinib was absorbed and bioavailable in 5 animal species tested.

Selpercatinib produced a 50% inhibitory concentration (IC_{50}) value of 1.1 μM in the Good Laboratory Practices (GLP) in vitro human ether-a-go-go (hERG) channel assay; no drug-related changes in any cardiovascular endpoint, including individual animal heart rate corrected QT intervals (QTcI) at doses up to 12 mg/kg in the cardiovascular study using conscious minipigs.

The toxicity of selpercatinib was evaluated in rats and minipigs in 14- and 28-day repeat dose, nonclinical studies. Dose groups were comprised of a vehicle control and low, medium, and high doses of selpercatinib. Rats and minipigs were chosen as appropriate test species for all in vivo toxicology studies based on PK and metabolic considerations.

Selpercatinib is currently being studied in an ongoing global Phase 1/2 first-in-human Study LOXO-*RET*-17001 in patients with advanced solid tumors including *RET* fusion-positive NSCLC, *RET*-mutant MTC, and other tumors with increased *RET* activity. As of a 30 March 2019 data cut-off date, safety data was available from 422 patients with 240 mg BID as the highest dose administered.

During dose escalation, 2 dose-limiting toxicities (DLTs) were reported, both at the 240 mg BID dose level: 1 DLT of Grade 3 tumor lysis syndrome and 1 DLT of Grade 3 thrombocytopenia. The remaining 4 patients treated at this dose level cleared the 28-day DLT window and continued on study. The dosage of 160 mg BID was selected as the recommended Phase 2 dose (RP2D) based on safety data (N = 82) and preliminary efficacy data in 64 evaluable patients treated at doses from 20 mg QD through 240 mg BID (Drilon et al. 2018).

Across 9 dose levels ranging from 20 mg QD to 240 mg BID in these 422 patients, TEAEs occurring in ≥15% patients were: dry mouth (30.8% total; 25.1% related), diarrhea (27.7% total; 12.8% related), hypertension (27.3% total; 16.8% related), fatigue (22.3% total; 14.5% related), constipation (21.8% total; 10.0% related), aspartate aminotransferase (AST) increased (21.6% total; 15.6% related), alanine aminotransferase (ALT) increased (20.4% total; 15.4% related), headache (18.7% total; 6.9% related), nausea (18.0% total; 6.6% related), edema peripheral (17.3% total; 9.5% related), and blood creatinine increased (14.9% total; 7.3% related).

A total of 205 (48.6%) patients across all dose levels experienced ≥Grade 3 TEAEs. Treatment-emergent adverse events of ≥Grade 3 that were considered to be related to study drug were reported in 95 (22.5%) patients across all dose levels. The most common Grade ≥3 TEAEs included hypertension (12.3%; 7.1% related), ALT increased (6.2%; 4.7% related), AST increased (4.7%; 3.1% related), hyponatremia (4.3%; 0.2% related), electrocardiogram (ECG) QT prolonged (2.8%; 2.1% related), dyspnea and lymphopenia (each 2.6%; 0% and 0.9% related, respectively), diarrhea and thrombocytopenia (each 2.1%; 0.7% and 1.7% related, respectively). All other Grade ≥3 TEAEs occurred in less than 2% of patients overall. Guidance on the management of hypersensitivity, liver test abnormalities, thrombocytopenia, and hypertension are provided in Section 6.6 and the IB.

As presented at World Conference on Lung Cancer (WCLC) 2018 and American Thyroid Association (ATA) 2018, with a data cutoff of July 19, 2018, the overall response rate (ORR) was 68% (95% confidence interval [CI] 51% to 83%, n = 26/38) in NSCLC, 78% (95% CI 40% to 97%, n = 7/9) in papillary thyroid cancer, 50% (n = 1/2) in pancreatic adenocarcinoma, 59% (95% CI 39% to 77%, n = 17/29) in MTC and 0% (n = 0/4) in patients without a known activating *RET* alteration in their cancers among the first 82 patients enrolled in Study LOXO-RET-17001. Updated interim results from the study are publicly available (Drilon et al. 2020; Wirth et al. 2020).

Additional information on the nonclinical pharmacology, PKs, and toxicity of selpercatinib are provided in the selpercatinib Investigator's Brochure (IB).

2.3. Benefit/Risk Assessment

Adult and adolescent patients with *RET*-mutant MTC comprise a population with high unmet need. Chemotherapy is ineffective for MTC. Therefore, there is an urgent need to identify new targeted therapies that potently inhibit *RET*-mutant MTC, while sparing other kinase and nonkinase off-targets that contribute to significant toxicity. Study JZJB is being conducted to confirm the benefit from selpercatinib seen in patients with advanced/metastatic MTC in the LIBRETTO-001 trial and to better understand this benefit in the context of other available treatments for advanced/metastatic MTC. As selpercatinib is a highly potent and specific inhibitor of the *RET* RTK with minimal inhibition of other kinase and nonkinase targets, there may be a potential benefit to adult and adolescent patients with MTC that harbor *RET* alterations and/or depend on *RET* activation.

The safety profile of selpercatinib is well-tolerated, clinically manageable, and distinct from available therapies, with the low rates of study drug discontinuation due to adverse events, particularly when compared to other TKIs such as cabozantinib or vandetanib. As outlined in the IB, the most common toxicities associated with selpercatinib are manageable and the majority of events were Grade 1 or 2.

Although the study procedures in Study JZJB are generally consistent with standard of care, increased monitoring of vital signs (including blood pressure), hematology, hepatic panels, and ECGs occur in the initial cycles to monitor for potential toxicities of interest. Additionally, an Independent Data Monitoring Committee (IDMC) will assess unblinded safety data during the trial on a regular basis. The IDMC will evaluate all safety-related data provided for each meeting to determine whether a change in the conduct of the trial is warranted for the safety of adult and adolescent patients.

Given its manageable toxicity profile and evidence of durable antitumor activity in patients with advanced *RET*-mutant MTC, selpercatinib may be of benefit in delaying treatment failure and disease progression and in improving survival in patients with progressive, advanced MTC who have not previously received cabozantinib or vandetanib. Therefore, the sponsor considers that the benefit/risk balance is positive and supports the proposed Phase 3 study, Study JZJB, exploring administration of selpercatinib in comparison to cabozantinib or vandetanib in adult and adolescent patients.

More information about the known and expected benefits, risks, serious adverse events (SAEs) and reasonably anticipated adverse events (AEs) of selpercatinib (LY3527723) may be found in the IB.

More detailed information about the known and expected benefits and risks of cabozantinib or vandetanib may be found in the following: Patient Information Leaflet, Package Insert, or Summary of Product Characteristics.

3. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To compare PFS of patients with progressive, advanced, kinase inhibitor naïve, *RET*-mutant MTC treated with selpercatinib versus cabozantinib or vandetanib.	• PFS by BICR
Secondary	
• To compare other efficacy outcomes, based on RECIST 1.1 criteria, observed in patients with progressive, advanced, kinase inhibitor naïve, *RET*-mutant MTC treated with selpercatinib versus cabozantinib or vandetanib.	• TFFS by BICR • TFFS by investigator • PFS by investigator • ORR by investigator and BICR • DoR by investigator and BICR • OS • PFS2 by investigator
• To evaluate the safety and tolerability of selpercatinib compared to cabozantinib or vandetanib.	• Safety per CTCAE v5.0 (including but not limited to): incidence and severity of TEAEs, SAEs, deaths, and clinical laboratory abnormalities.
• To compare the tolerability of selpercatinib versus cabozantinib or vandetanib	• Proportion of time with high-side-effect bother based on FACT-GP5
• To assess/evaluate performance of local *RET* laboratory tests compared to a single, central test.	• *RET* mutation status
• To assess the PK of selpercatinib in patients receiving selpercatinib.	• Predose plasma concentrations at Day 8 of Cycle 1, and at Day 1 of Cycles 2 through 6.
Exploratory	
• To compare the calcitonin and CEA response rate of patients with progressive, advanced, kinase inhibitor naïve, *RET*-mutant MTC treated with selpercatinib versus cabozantinib or vandetanib.	• Calcitonin response rate • CEA response rate

Objectives	Endpoints
Exploratory	
• To compare the PROs of disease-related symptoms, symptomatic adverse events and overall side effect burden, physical function, and HRQoL of patients with progressive, advanced, kinase inhibitor naïve, *RET*-mutant MTC treated with selpercatinib versus cabozantinib or vandetanib.	• Bristol Stool Form Scale and bowel movement frequency • Physical Function (EORTC IL19) • HRQoL (EORTC QLQ-C30) • Health Utilities (EQ-5D-5L) • Worst Pain NRS • Patient-reported AEs (PRO-CTCAE)
• To assess the efficacy and safety of selpercatinib in patients assigned to Arm B who crossover to selpercatinib after progression	• PFS after crossover • Safety per CTCAE v5.0 after crossover (including but not limited to) o incidence and severity of TEAEs o SAEs o deaths, and o clinical laboratory abnormalities.
• To compare the TTNT of patients with progressive, advanced, kinase inhibitor naïve, *RET*-mutant MTC treated with selpercatinib versus cabozantinib or vandetanib.	• TTNT
• To compare *RET* mutation status in tumor and circulating free tumor DNA (cfDNA) samples.	• Biomarker analyses
• To assess the relationship between biomarkers and clinical outcomes	• Biomarkers assessed from blood or tissue samples, unless precluded by local regulations • Clinical outcomes data

Abbreviations: BICR = blinded independent review committee; CEA = carcinoembryonic antigen; CTCAE = Common Terminology Criteria for Adverse Events; DNA = deoxyribonucleic acid; DoR = duration of response; FACT-GP5 = Functional Assessment of Cancer Therapy-Side Effects; EORTC-QLQ30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 Version 3.0; EORTC IL19 = European Organisation for Research and Treatment of Cancer, item library 19; EQ-5D-5L = 5-level-EuroQol; HRQoL = health-related quality of life; MTC = medullary thyroid cancer; NRS = numeric rating scale; ORR = overall response rate; OS = overall survival; PFS = progression free survival; PFS2= progression-free survival 2; PK = pharmacokinetics; PRO = patient reported outcomes; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; TEAE = treatment-emergent adverse event; TFFS = treatment failure-free survival; TTNT = time to initiation of new anticancer therapy.

4. Study Design

4.1. Overall Design

This is a global, multicenter, randomized (2:1), open-label, Phase 3 study comparing selpercatinib (treatment Arm A) to physician's choice of cabozantinib or vandetanib (treatment Arm B) in patients with progressive, advanced, kinase inhibitor naïve, *RET*-mutant MTC.

Patients will be randomized in a 2:1 ratio to selpercatinib or physician's choice of cabozantinib or vandetanib.

Patients will be stratified based on:

- *RET* mutation: M918T vs. other
- Intended treatment if randomized to control arm: cabozantinib vs. vandetanib.

Approximately 250 patients will be initially enrolled to the study. A sample size re-estimation based on comparative data will be conducted at the interim efficacy analysis. The total number of patients could be increased from the initially planned 250 up to a maximum of approximately 400 depending on the results of the interim efficacy analysis.

Patients with histologically confirmed, unresectable, locally advanced or metastatic MTC who have not received previous treatment with a kinase inhibitor are eligible for enrollment in this study. Patients are required to have radiologic progressive disease per RECIST 1.1 at screening compared with an image obtained within the prior 14 months. Patients are also required to have a documented *RET* mutation (Appendix 6) in tumor or germline DNA identified through molecular assays. The *RET* result should be generated from a laboratory with certification by Clinical Laboratory Improvement Amendments (CLIA), International Organization for Standardization/Independent Ethics Committee (ISO/IEC), College of American Pathologists (CAP), or other similar certification. In regions or at sites where *RET* is not standard of care and/or an acceptable local test (as defined by Lilly) is not available, a pre-screening consent will be used to provide the patient with a sponsor-supported testing option to determine tumor *RET* status. In addition, the sponsor or it's designee will review all imaging to confirm progressive disease per RECIST 1.1 in the prior 14 months and all molecular pathology reports to confirm the presence of a valid *RET* alteration prior to enrollment.

After confirmation of eligibility, patients will be randomized in a 2:1 ratio to receive selpercatinib at a starting dose of 160 mg BID (treatment Arm A), cabozantinib at a starting dose of 140 mg QD (treatment Arm B1), or vandetanib at a starting dose of 300 mg QD (treatment Arm B2). Adolescent participants will have weight-based dosing as outlined in Section 6.1. The selection of cabozantinib or vandetanib for each eligible patient is required by the investigator prior to randomization and will be documented in the Interactive Web Response System (Study Schema Section 1.2). This selection is a stratification factor. Up to 2 dose reductions for treatment-related toxicity (see Section 6.6) will be allowed. Dosing will be in oral capsule/tablet form.

Treatment will continue until disease progression, unacceptable toxicity, or death. The treatment decision will be made by investigator assessment (see Section 7). Patients with disease progression per investigator assessment may continue treatment while awaiting BICR confirmation of progression.

Patients discontinuing treatment for any reason other than death, lost to follow-up, or withdrawal of consent will enter the survival follow-up period and be followed every 3 months for the development of radiographic disease progression (if not already occurred) and initiation of subsequent anti-cancer therapies (as allowed by their next treatment regimen [see Section 8.1.1 for additional details]) until death, lost to follow-up, or withdrawal of consent (whichever comes first).

Patients who discontinue treatment and who have radiographic disease progression that is confirmed by BICR and were randomized to cabozantinib or vandetanib may be eligible for crossover to selpercatinib if they meet the eligibility criteria for crossover (see Section 5.2.1). The primary endpoint, progression free survival (PFS) by BICR, will act as a gatekeeper for the key secondary endpoints of treatment failure-free survival (TFFS) by BICR and comparative tolerability, i.e., these key secondary endpoints will be tested conditionally on achieving a statistical significance for the primary endpoint. TFFS will act as a gatekeeper for another key secondary endpoint of comparative tolerability.

4.2. Scientific Rationale for Study Design

Selpercatinib is a highly potent and specific small molecule inhibitor of the *RET* kinase, with minimal inhibition of other kinase and non-kinase targets.

Given its manageable toxicity profile and evidence of durable antitumor activity in patients with advanced *RET* mutant MTC, selpercatinib may be of benefit in delaying treatment failure and disease progression and improving survival in patients with progressive, advanced MTC who have not previously received cabozantinib or vandetanib. PFS was selected as the primary endpoint. A key secondary endpoint of TFFS was selected as this endpoint takes into account potential improvement in both efficacy and toxicity profile relative to comparator agents. The key secondary endpoint of TFFS will be type I error-controlled.

Another key secondary type I error-controlled endpoint is the comparative tolerability defined as a comparison of the proportion of time on treatment with a high side effect burden as assessed by the single item Functional Assessment of Cancer Therapy - Side Effects (FACT-GP5) instrument. This endpoint allows evaluation of the patient's perception of tolerability, in particular the burden of side effects while on treatment, to understand if the improvement in tolerability further supports the clinical benefit of selpercatinib.

With PFS as the primary endpoint, TFFS and comparative tolerability as key secondary endpoints, and additional steps taken to maximize the robustness of these endpoints, the sponsor believes the study design has the potential to generate a timely and clinically important result that elucidates both safety and efficacy differences of selpercatinib and cabozantinib or vandetanib.

The choice of control arm agent, either cabozantinib or vandetanib, is allowed due to regional differences in the standard of care in this global trial. Options in the treatment for the control arm also minimizes the number of patients that have to be excluded due to medical conditions (which is critical in this trial in an extremely rare disease state) as the medical exclusions for cabozantinib and vandetanib do not overlap greatly.

An open-label study design was selected since the AE profile of the comparator agents, cabozantinib and vandetanib, differ greatly and thus it would be impractical to blind the patients

or investigators to treatment arm. Additionally, as the dosing schedule and number of pills vary for each of the 3 treatment regimens, patients could conceivably be confused by the regimens and over or underdose their active agent.

There is significant uncertainty as to the performance of both treatment arms: Arm A and Arm B. Specifically:

- Monitoring of MKI-naïve patients participating in LIBRETTO-001 provides some insight into the potential outcomes of patients treated with selpercatinib on Arm A. Reliable prediction of median PFS for Arm A based on the LIBRETTO-001 data is challenging due to the immature data with a high censoring rate at the time of protocol amendment.
- Arm B uses two drugs with very large differences in reported median PFS time. It is unclear if the differences are due to differences in the treated population, inherent differences in drug effects, or both. However, these factors all contribute to the uncertainty of estimating median PFS for Arm B.
    - In the EXAM study, the median PFS was 11 months for cabozantinib-treated patients with documented progression within 14 months of treatment enrollment (irrespective of the presence of a *RET* mutation) (Elisei et al. 2013, Schlumberger et al. 2017), and was longer (13.9 months) for the subset of patients with cancers harboring *RET* M918T mutations (the most common *RET* mutation) (Sherman et al. 2016).
    - In the ZETA study, the median PFS was 30.5 months for vandetanib-treated patients with newly diagnosed advanced MTC and patients with progression (Wells et al. 2012). A post hoc analysis provided median PFS results for two subgroups of patients that are similar to those enrolling in Study JZJB based on the presence of progressive disease within 12 months of enrollment. For those with both disease progression and symptoms in the prior 12 months, median PFS was 21.4 months and for those with disease progression only in the prior 12 months, median PFS was not reached at a median follow-up of 95 months (Kreissel et al. 2020).

An adaptive design with sample size re-estimation based on comparative data at the interim efficacy analysis is selected to mitigate the uncertainties of the true treatment effect by allowing the study to adjust to information that is currently not available.

Patients randomized to the control arm will be allowed to crossover to receive the investigational product at the time of BICR confirmed radiographic progression. This will allow patients access to a highly specific *RET*-inhibitor after progression on an MKI. It will also add to the amount of safety and efficacy data for selpercatinib in the second line setting in this difficult to enroll population (due to rarity of disease).

4.3. Justification for Dose

4.3.1. Selpercatinib

Based on preclinical pharmacology experiments with human cancer cells in vitro and in murine xenograft models, meaningful inhibition of *RET* in tumors is expected to be achievable with oral

dose regimens at total daily doses ≥40 mg/day. The dosage of 160 mg BID was selected as the RP2D based on safety data (N=82) and preliminary efficacy data in 64 evaluable patients treated at doses from 20 mg QD through 240 mg BID (Drillson et al 2018, NCT03157128). Additional information is provided in Section 2.2.1 and in the selpercatinib IB.

4.3.2. Cabozantinib

The cabozantinib starting dose of 140 mg daily is the globally approved dose for adult patients with MTC, based on the results of the Phase 3 EXAM trial in patients with progressive MTC (Elisei et al 2013). Despite the toxicity observed at this dose, there is no evidence that a lower dose is safer or equally effective. An ongoing study of 2 different doses of cabozantinib (60 mg daily and 140 mg daily) is examining whether a lower dose is has equivalent PFS and fewer AEs in MTC patients (NCT01896479). Available data for a lower dose in patients with renal cell carcinoma (RCC) from the CABOSUN trial and hepatocellular carcinoma in the CELESTIAL trial indicates that the percentage of patients experiencing AEs (any grade or Grade ≥3) and dose reductions or discontinuations for AEs are similar between RCC patients who received 60 mg daily and MTC patients who received 140 mg daily (Choueiri et al 2018; Abou-Alfa et al 2018). Existing guidelines for MTC patients indicate that whether a lower starting dose is more reasonable remains an unresolved question (Wells et al 2015). For these reasons, the starting dose of cabozantinib in the current study is 140 mg daily. Cabozantinib was assessed in a Phase 1 study in a Children's Oncology Group study in pediatric/adolescent participants with recurrent or refractory solid tumors, including CNS tumors. The dose recommended for further evaluation (40 mg/m2/d) will be used in Study JZJB (Chuk et al 2018).

4.3.3. Vandetanib

The vandetanib starting dose of 300 mg daily is the globally approved dose for patients with MTC, based on the results of the Phase 3 ZETA trial in patients with unresectable locally advanced or metastatic disease (Wells et al. 2012). Despite the toxicity observed at this dose, there is currently no evidence that a lower dose is safer or equally effective. Existing guidelines for MTC patients indicate that whether a lower starting dose is more reasonable remains an unresolved question (Wells et al 2015). In a Phase I/II study in pediatric/adolescent participants the vandetanib C_{ss} in children receiving 100 mg/m2/d was similar to the C_{ss} in adults receiving the recommended adult dose of 300 mg (Fox et al. 2013). As a result, 100 mg/m2/d was recommended as the dose for further study in adolescent patients with locally advanced or metastatic MTC. In Study JZJB doses will be administered as outlined in Section 6.1.

4.4. End of Study Definition

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 SoAs for the last participant in the trial globally.

The total study duration will be capped at 6 years from the first patient visit. A duration of 6 years is considered to be a relevant timeframe considering that the treatment landscape may change substantially and continuation on study follow-up may present an undue burden on participants.

5. Study Population

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. Are of an acceptable age to provide informed consent according to local regulations and are at least 18 years of age (patients as young as 12 years of age will be allowed if permitted by local regulatory authorities and institutional review boards).
    a. All patients of 12 years of age and older, after giving assent / legally designated representative/ participant written consent.

Type of Participant and Disease Characteristics

2. Histologically or cytologically confirmed, unresectable, locally advanced and/or metastatic MTC and no prior history of treatment with kinase inhibitors for advanced/metastatic disease.
    a. Prior systemic (agents other than kinase inhibitors) or radiation therapy occurring >14 months before enrollment is allowed. Prior systemic therapy or radiation therapy within the 14 months before enrollment may be allowed with discussion and approval by the Lilly medical team.
    b. Patients with prior kinase inhibitor therapy of less than 7 days and discontinued for reasons other than intolerance or progression may be allowed with approval by the Lilly medical team.
    c. Patients with mixed histology (e.g., incidental papillary thyroid cancer identified at the time of resection) are eligible if MTC is the dominant histology.
3. Radiographic progressive disease per RECIST 1.1 (Eisenhauer et al. 2009) at screening compared with a previous image taken within the prior 14 months as assessed by the BICR. Patients with measurable or non-measurable but evaluable disease are eligible; however, patients with non-measurable disease may not have disease limited to bone sites only.
4. A *RET* gene alteration identified in a tumor, germline DNA or blood sample (for example, circulating free DNA [cfDNA]), as defined in Appendix 6. The *RET* alteration result should be generated from a laboratory with CLIA, ISO/IEC, CAP, or other similar certification. Lilly should be contacted to discuss test results from labs where such certification is not clearly demonstrated to determine eligibility; if certification is not required in the patient's country, the Sponsor may allow enrollment using a result from a non-certified lab if sufficient evidence can be provided as to the accuracy of the result. A positive germline test for a *RET* mutation is acceptable given the test was determined by internal institutional quality standards and performed for clinical evaluation. In all cases, a redacted Molecular Pathology Report or other report(s) describing *RET* (and any co-

occurring findings, if applicable) alteration analysis should be submitted to Lilly or designee during/prior to eligibility.

a. Mandatory provision of an unstained, archived tumor tissue sample in a quantity sufficient to allow for retrospective central analysis of *RET* mutation status (for confirmation). Please refer to Section 8.8.1 for details.

5. Eastern Cooperative Oncology Group (ECOG) performance status score (Oken et al. 1982) of 0 to 2.
6. Ability to swallow capsules and comply with treatment, laboratory monitoring, and required clinic visits for the duration of study participation.
7. Patients must have discontinued from previous treatments as shown below and fully recovered. Consult with the Lilly medical team for the appropriate length of time prior to the first dose of study treatment on additional therapies not mentioned.

Previous Treatment	Length of Time Prior to First Treatment Dose
Radiotherapy (full field or if ≥25% bone marrow irradiated	within ≥28 days
Limited field radiotherapy (i.e., <25% bone marrow affected)	≥14 days
Major surgery, excluding biopsy and placement of vascular access	≥28 days if patient is intended to receive cabozantinib vs selpercatinib ≥14 days if patient is intended to receive vandetanib vs selpercatinib

8. Have adequate organ function, as defined below:

System	Laboratory Value
Hematologic	
ANC[a]	≥1.5×10^9/L
Platelets	≥100×10^9/L
Hemoglobin	≥9 g/dL
Note: transfusions to increase a patient's hemoglobin level or initiation of erythropoietin or G-CSF therapy to meet enrollment criteria are not allowed in the 7 days preceding the first dose of study drug. If a patient receives transfusions, erythropoietin, or G-CSF therapy ≥7 days prior to the first dose, the hematologic criteria listed above must be met following the 7 day window prior to the first dose of study therapy.	
Hepatic	
Total bilirubin	≤1.5× ULN **OR** <3.0 x ULN for patients who have Gilbert's syndrome
ALT and AST	≤2.5 × the upper limit of normal (ULN) **OR** ≤5× ULN if the liver has tumor involvement
Renal	
Creatinine clearance	≥30 mL/min

a Patients with a demonstrated history of benign ethnic neutropenia (Hsieh 2010) may be enrolled with lower ANC with approval from the Lilly medical team.

9. Patients must have serum potassium, calcium, and magnesium levels above the lower limit of normal (may be receiving supplements) and not clinically significantly above the upper limit of normal.

Sex

10. Men with partners of childbearing potential or women of childbearing potential must agree to use a highly effective contraceptive method (for example, intrauterine device [IUD], birth control pill, or barrier method) during treatment with study drug and for 4 months following the last dose of study drug. See Appendix 3.

    Note: Unless not allowed by local regulations, women 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 unless they agree to use contraceptive method known to be highly effective. Periodic abstinence (e.g., calendar, ovulation, symptothermal, postovulation methods), declaration of abstinence just for the duration of a trial, and withdrawal are not acceptable methods of contraception.

11. Women of childbearing potential must
    - have a negative pregnancy test (serum or urine, consistent with local regulations) documented within 24 hours prior to treatment with study drug.
    - not be breast-feeding during treatment and for at least 4 months after the last dose of study drug.

Informed Consent

12. Capable of giving signed informed assent/consent as described in Appendix 1 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol

5.2. Exclusion Criteria

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

Medical Conditions

13. An additional validated oncogenic driver in MTC if known that could cause resistance to selpercatinib treatment. Examples include, but are not limited to *RAS or BRAF* gene mutations and *NTRK* gene fusions.
14. Symptomatic CNS metastases, leptomeningeal carcinomatosis, or untreated spinal cord compression. Patients are eligible if neurologically stable and without increase in steroid dose for 14 days prior to the first dose of study treatment and no CNS surgery or radiation has been performed for 28 days, 14 days if stereotactic radiosurgery (SRS).
15. Clinically significant active cardiovascular disease or history of myocardial infarction within 6 months prior to planned start of study treatment, history of Torsades de pointes, or prolongation of the QT interval corrected for heart rate using Fridericia's formula (QTcF) >470 msec on more than one ECG during Screening. Correction of suspected

drug-induced QTcF prolongation may be attempted at the investigator's discretion if clinically safe to do so. Patients who are intended to receive vandetanib if randomized to the control arm are ineligible if QTcF is >450 msec.

a. **Note:** Patients with implanted pacemakers may enter study without meeting QTc criteria due to nonevaluable measurement if QT changes are considered monitorable

b. **Note:** Patients with bundle branch block may be considered for study entry if QTc is appropriate by a formula other than Fridericia's and if QT changes are considered monitorable.

16. Active uncontrolled systemic bacterial, viral, or fungal infection or serious ongoing intercurrent illness, such as hypertension or diabetes, despite optimal treatment, a clinical diagnosis or symptoms of interstitial lung disease (ILD), or other serious medical conditions which in the medical judgment of the investigator would prevent the patient from safely participating (screening for chronic conditions is not required).
17. Clinically significant active malabsorption syndrome or other condition likely to affect gastrointestinal absorption of the study drug.
18. Uncontrolled symptomatic hyperthyroidism or hypothyroidism
19. Uncontrolled symptomatic hypercalcemia or hypocalcemia
20. Active hemorrhage or at significant risk for hemorrhage.
21. Other malignancy unless nonmelanoma skin cancer, carcinoma in situ or malignancy diagnosed ≥2 years previously and not currently active. Patients receiving adjuvant hormone therapy for breast or prostate cancer with no evidence of disease are eligible. Participants with MEN2-associated pheochromocytoma are eligible if the pheochromocytoma is, in the opinion of the investigator, documented to be stable or has been resected (and patient has fully recovered from surgery).

Prior/Concomitant Therapy

22. Prior systemic treatment with kinase inhibitor(s) (Refer to Section 5.1, Inclusion Criterion 2b).
23. Are taking a concomitant medication that is known to cause QTc prolongation (for examples, see Appendix 7).

Prior/Concurrent Clinical Study Experience

24. Have participated, within the last 30 days (4 months for studies conducted in Japan; 3 months for studies conducted in the UK), in a clinical study involving an investigational product. If the previous investigational product has a long half-life, 5 half-lives or 30 days (4 months for studies conducted in Japan; 3 months for studies conducted in the UK) (whichever is longer) should have passed. Exceptions will be considered on a case by case basis by the Lilly medical team.

Other Exclusions

25. Life expectancy ≤3 months

26. Have a known hypersensitivity to any of the excipients of selpercatinib, cabozantinib, or vandetanib.

5.2.1. Eligibility Criteria for Crossover Treatment

A crossover to selpercatinib will be allowed only at radiographic disease progression confirmed by BICR. In order for participants to crossover to selpercatinib, they must meet the following criteria.

Eligibility criteria for crossover to selpercatinib:

a) Radiographic PD by RECIST 1.1 as assessed by BICR
b) Willing and able to provide written informed consent to crossover
c) Adequate hematologic, hepatic, and renal function as defined above for initial eligibility
d) All toxicities attributed to cabozantinib or vandetanib have resolved or decreased to Grade 1
e) Remains ECOG 0-2
f) Has discontinued cabozantinib or vandetanib and has not received any other systemic therapy since

Patients are eligible to be considered for crossover if:

- they meet the criteria above and
- can initiate treatment with selpercatinib after a minimum of 15 days and within 42 days the time of BICR confirmed progression.

No exceptions will be made for eligibility criterion a. However, other exceptions may be made on a case-by-case basis following approval from the sponsor.

Patients that may crossover should **not**:

- complete V801 at the end of their initial treatment, but should enter V201 and/or V300 prior to starting selpercatinib (Section 1.3, SoA). Visit 201 will allow for the collection of Arm B post-treatment safety information for patients that do not cross over to selpercatinib within 30 (+/-7 days) of the last dose of study treatment.
- initiate selpercatinib any earlier than 21 days after their last dose of study treatment.

5.3. Lifestyle Considerations

There are no specific lifestyle restrictions for Study JZJB, other than as noted in Inclusion Criteria 10.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Rescreened participants should be assigned a new participant number. The interval between rescreening should be ≥2 weeks. Each time rescreening is performed, the individual must sign a new ICF and will be assigned a new identification number. 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 medicinal product(s) or medical device(s) intended to be administered to or used by a study participant according to the study protocol.

6.1. Study Intervention(s) Administered

A cycle is defined as 28 days in length with treatment on days 1 through 28 of each cycle, regardless of treatment arm assignment. A delay of the start of a cycle due to holiday, weekend, bad weather, or other unforeseen circumstances will be permitted for a maximum of 7 days or situations noted in Section 10.1.9 and not counted as a protocol deviation. Cycles should not be delayed for AEs. If needed for AEs, doses should be omitted within a cycle. Treatment should be initiated within 7 days of randomization.

Regardless of treatment arm, drug will initially be dispensed as a 28-day supply. For adult patients remaining on treatment after Cycle 15, drug will be dispensed as an 84-day supply, starting at Cycle 16.

Selpercatinib doses will be administered at approximately the same times on each day and BID dosing will be separated by approximately 12 hours (a minimum of 6 hours between consecutive doses). Selpercatinib can be taken with or without food. Cabozantinib or vandetanib will be administered at approximately the same time on each day. Cabozantinib should be taken without food; patients should not eat for at least 2 hours before and at least 1 hour after each dose. Vandetanib can be taken with or without food.

All patients will keep a daily diary to record dosing compliance, which will also be assessed at each clinic visit by means of a capsule count in the returned bottle(s). Late doses (i.e., 4 or more hours after scheduled time for selpercatinib) should be noted in the diary. Doses of selpercatinib that are late by more than 6 hours and doses of cabozantinib or vandetanib that are late by more than 12 hours should be skipped and recorded in the dosing diary as missed. Vomiting after dosing should be noted in the diary and a vomited dose should not be re dosed or replaced.

6.1.1. Adult Dosing

	Arm A	Arm B1	Arm B2
Intervention	Selpercatinib	Cabozantinib	Vandetanib
Adult Dose	160 mg BID	140 mg QD	300 mg QD[a]
Authorized as defined by EU Clinical Trial Regulation	Authorized and used according to EU authorization	Authorized and not used according to EU authorization	Authorized and used according to EU authorization

Abbreviations: BID = twice daily; QD = once daily.

[a] Starting dose of vandetanib should be 200 mg in patients with moderate renal impairment (creatinine clearance results between 30 and 50 mL/min). In case vandetanib 100-mg tablets are not available, see Section 6.6.

6.1.2. Adolescent Dosing

	Arm A	Arm B1	Arm B2
Intervention	Selpercatinib	Cabozantinib	Vandetanib
Adolescent Dose[a] Approximate adult equivalent dose	92 mg/m^2 BID (not to exceed 160 mg BID) 160 mg BID	40 mg/m^2 72 mg QD	See dosing guide
Authorized as defined by EU Clinical Trial Regulation	Authorized and used according to EU authorization	Authorized and not used according to EU authorization	Authorized and used according to EU authorization

Abbreviations: BID = twice daily; QD = once daily.

[a] Please refer to nomograms below for the exact dosing.

Adolescent patients will have BSA-adjusted dosing as outlined in the tables below. BSA should be determined according to the Mosteller Formula (Mosteller 1987).

Selpercatinib

Selpercatinib dosing will be rounded according to guidelines in the table below. The maximum starting dose will be no higher than 160 mg BID.

Selpercatinib Capsule Dose Rounding (all doses BID)

BSA (m^2)	Rounded Dose (mg)
<0.76	40 mg
0.76 – <1.2	80 mg
1.2 – <1.6	120 mg
≥1.6	160 mg

Abbreviations: BSA = body surface area.

Vandetanib

Vandetanib Dosing Nomogram for Adolescent Participants

BSA (m^2)	Start dose (mg)[a]
0.7 - <0.9	100 QOD
0.9 - <1.2	100 QD

BSA (m^2)	Start dose (mg)[a]
1.2 - <1.6	7 day schedule: 100-200-100-200-100-200-100
≥1.6	200 QD

Abbreviations: BSA = body surface area; QD = once daily; QOD = once every other day.

[a] A reduced starting dose of vandetanib should be used in adolescent patients with moderate renal impairment as per the dose reduction table in Section 6.6.

Cabozantinib

Cabozantinib Dosing Nomogram for Adolescent Participants

BSA (m^2)	Weekly Dose/ Schedule for Initial Dosing
0.35 – 0.39	100 mg = 20 mg M, W, Th, Sat, Sun
0.40 – 0.45	120 mg =20 mg M, T, W, F, Sat, Sun
0.46 – 0.55	140 mg =20 mg QD
0.56 – 0.64	160 mg = 40 mg M, W, F, Sun
0.65 – 0.78	200 mg = 40 mg M, W, Th, Sat, Sun
0.79 – 0.90	240 mg = 40 mg M, T, W, F, Sat, Sun
0.91 – 1.09	280 mg = 40 mg QD
1.10 – 1.17	300 mg = 60 mg M, W, Th, Sat, Sun
1.18 – 1.36	360 mg = 60 mg M, T, W, F, Sat, Sun
1.37 – 1.65	420 mg = 60 mg QD
1.66 – 1.85	480 mg = 80 mg M, T, W, F, Sat, Sun
1.86 – 2.07	560 mg = 80 mg QD
≥ 2.08	600 mg = 100 mg M, T, W, F, Sat, Sun

Abbreviations: BSA = body surface area; QD = once daily.

6.1.3. Exceptional Switch from Vandetanib to Cabozantinib

Participants assigned to the control arm should not switch between control arm treatments. In exceptional situations where vandetanib is not available:

- participants originally assigned to vandetanib may be allowed to switch to cabozantinib during the study.
- physician's choice in the control arm may be limited to cabozantinib only.

If vandetanib is not available and participant fulfills the eligibility criteria listed in Section 6.1.3.1, the participant may be allowed to switch to cabozantinib.

If participant is on reduced dose level of vandetanib due to toxicities, then the corresponding dose level should be considered for starting dose of cabozantinib at switch.

6.1.3.1. Eligibility Criteria for Switching from Vandetanib to Cabozantinib

A switch from vandetanib to cabozantinib will be allowed if study intervention supply is unavailable and after approval by study sponsor.

Conduct safety assessments more frequently during the first 3 cycles of switch treatment. See SoA table, Section 1.3.3.

Eligibility criteria for switching from vandetanib to cabozantinib:

a) Willing and able to provide written informed consent to switch.
b) No ongoing AEs impacting hematologic, hepatic, and renal function > G2.
c) Participant has not previously discontinued due to vandetanib-related AE.
d) All toxicities attributed to vandetanib have resolved or decreased to Grade 1.
e) Has discontinued vandetanib for a minimum of 15 days and up to 42 days before treatment with cabozantinib is initiated.
f) Participant has no disease progression by investigator assessment.

Exceptions to criteria b may be made on a case-by-case basis, following approval from the sponsor.

6.1.4. Packaging and Labeling

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

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received, as appropriate, 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 staff may administer study intervention and/or supply study intervention to participant. 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. Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy Manual.
5. Investigators should consult the study drug information provided in the Pharmacy Manual or label for the specific administration information (including warnings, precautions, contraindications, adverse reactions, and dose modifications).

6.3. Measures to Minimize Bias: Randomization and Blinding

This is an open-label study. However, to preserve the integrity of the trial, Lilly will not have unblinded access to aggregate data from the clinical database. An Independent Data Monitoring Committee (IDMC) will evaluate aggregate interim efficacy results to provide recommendations of adaptation at the interim analysis and monitor aggregate safety data during the course of the trial on a regular basis. An external Statistical Analysis Center will conduct interim efficacy and safety analyses and report the results to the IDMC. This practice will ensure that Lilly personnel involved in the day-to-day management and conduct of the trial do not have access to unblinded comparative results, even inadvertently. Additional details are specified in Section 9.5 and separate IDMC and Adaptive Design Charters.

To maintain the trial integrity after the sample size re-estimation, other measures will be taken to avoid disclosure of the interim comparative results:

- Any members of the study team that have access to the adaptation decision will be prespecified and documented. Other Lilly study team members will be shielded as much as possible from the knowledge of adaptive changes.
- The adaptation algorithm and details on the sample size re-estimation will be preserved in an Adaptive Design Charter and stored confidentially in a restricted access area. Only the IDMC, SAC and the Lilly statisticians involved in the adaptive design will have access to the Adaptive Design Charter. No other study team members will have access.
- Investigators and trial participants will not be provided with any details regarding an adaptive decision. For example, if the study will continue (sample size may or may not increase) after the interim efficacy analysis, they will be informed that the targeted patient/event number hasn't been reached rather than being notified of the specific targeted final sample size/number of events. Lilly personnel who have direct interaction with study sites will be appropriately trained on this expectation.

More detailed actions to maintain the trial integrity will be described in the Statistical Analysis Plan.

To minimize investigator bias on the efficacy assessment, the primary endpoint of PFS will be determined based on the assessment of a BICR (see Section 8.1.2). Patients on Arm B will be allowed to cross over to selpercatinib only after progression has been confirmed by the BICR. Details of the BICR will be described in a separate BICR Charter.

6.4. Study Intervention Compliance

Participant compliance with study intervention will be assessed at each visit. Compliance will be assessed by direct questioning, counting returned tablets/capsules, and reviewing patient diaries. Deviation(s) from the prescribed dosage regimen should be recorded in the eCRF.

A participant will be considered noncompliant if he or she takes <75% of the planned doses for assigned study drug in a cycle. A participant will also be considered noncompliant if he or she is judged by the investigator to have intentionally or repeatedly taken ≥125% of the planned doses of study drug in a cycle.

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.

Patients receiving selpercatinib should avoid concomitant use of CYP2C8-sensitive substrates. If co-administration of a CYP2C8-sensitive substrate cannot be avoided, monitor patients for increased adverse reactions of these drugs.

Caution should be used when co-administration of a P-gp substrate (for example, fexofenadine, loperamide, and digoxin), MATE1 substrate (for example, metformin), or BCRP substrate (for example, sulfasalazine) cannot be avoided in patients receiving selpercatinib. Consider increased monitoring as appropriate. The concurrent use of drugs known to prolong QTc is prohibited (Appendix 7). Drugs with a possible or conditional risk should be avoided if possible. Patients eligible to receive vandetanib should refrain from sun exposure during and up to 4 months after discontinuation of treatment due to possible photosensitivity.

The Lilly medical team should be contacted if there are any questions regarding concomitant or prior therapy. Except as indicated in Section 6.1, patients are not allowed to receive concomitant systemic anti-cancer agents (including immunotherapy agents), hematopoietic growth factors for prophylaxis in C1, drugs with immunosuppressant properties (other than as listed in Section 6.5.4), or any other investigational agents. No new, alternative systemic anticancer therapy is allowed prior to documentation of PD in accordance with protocol specified disease response criteria. No surgical resection of tumor or radiation therapy is permitted except as described in Section 6.5.4.

6.5.1. CYP3A4 Inducers or Inhibitors

For patients receiving selpercatinib: The concomitant use of the strong CYP3A4 inhibitors or inducers should be avoided. See Appendix 7.

If, during the study, patients require initiation of treatment with strong inhibitors or inducers of CYP3A4 for clinical reasons, investigators should consider increased monitoring for the development of new AEs.

Co-administration of selpercatinib with sensitive CYP3A4 substrates may increase their plasma concentrations, which may increase the incidence or severity of adverse reactions for sensitive substrates with narrow therapeutic windows.

For patients receiving cabozantinib: The concomitant use of strong inhibitors or inducers of CYP3A4 should be avoided. If strong CYP3A4 inhibitors cannot be avoided, the cabozantinib dose should be reduced by 20 mg daily; if the CYP3A4 inhibitor is to be discontinued, the regular dose cabozantinib should be resumed 2 to 3 days after discontinuation of the strong inhibitor. If strong CYP3A4 inducers cannot be avoided, the cabozantinib dose should be increased by 20 mg daily; if the CYP3A4 inducer is to be discontinued, resume the regular dose of cabozantinib 2-3 days after discontinuation of the strong inducer. See Appendix 7.

For patients receiving vandetanib: The concomitant use of strong inducers of CYP3A4 should be avoided. See Appendix 7.

6.5.2. Agents That Alter Gastric Acidity (PPIs and H2 blockers)

Since selpercatinib absorption from the gastrointestinal tract may be impacted by stomach acidity, concomitant use of pH-altering agents require additional instructions for patients randomly assigned to treatment arm A.

Avoid concomitant use of a PPI, H2 receptor antagonist, or a locally-acting antacid with selpercatinib. If concomitant use cannot be avoided,

- Take selpercatinib with food (at least 400 calories) when co-administered with a PPI.
- Take selpercatinib 2 hours before or 10 hours after administration of an H2 receptor antagonist.
- Take selpercatinib 2 hours before or 2 hours after administration of a locally-acting antacid.

There are no restrictions on PPI or H2 blocker use for patients randomized to the control arm and who are receiving cabozantinib or vandetanib.

6.5.3. P-gp Substrates or MRP2 Inhibitors

Cabozantinib and Vandetanib may have the potential to increase plasma concentrations of co-administered substrates of P-gp (e.g., fexofenadine, aliskiren, ambrisentan, dabigatran etexilate, digoxin, colchicine, maraviroc, posaconazole, ranolazine, saxagliptin, sitagliptin, talinolol, tolvaptan). Therefore, appropriate clinical (e.g., ECG) and/or laboratory monitoring is recommended for patients receiving concomitant digoxin and such patients may require a lower dose of digoxin. Appropriate clinical monitoring is recommended for patients receiving other P-gp substrates such as dabigatran when given in combination with vandetanib or cabozantinib.

Similarly, the administration of MRP2 inhibitors (e.g., cyclosporine, efavirenz, emtricitabine) may result in increases in cabozantinib plasma concentrations. The use of MRP2 inhibitors should be approached with caution.

6.5.4. Palliative Medicine and Supportive Care

Standard supportive medications may be used in accordance with institutional guidelines and Investigator discretion. The use of granulocyte-colony stimulating factor (G-CSF) is permitted at the discretion of the investigator based on American Society of Clinical Oncology (ASCO) (Smith et al. 2015) and European Society for Medical Oncology (Crawford et al. 2009) guidelines, though may not be used prophylactically in Cycle 1.

If clinically indicated at any time during the study, erythropoietin and packed red blood cell transfusions may be used according to ASCO guidelines (Rizzo et al. 2008). Prophylactic antibiotic treatment should be consistent with ASCO guidelines (Flowers et al. 2013).

Continuation of standard of care medications, including anti-emetic, analgesic, and antidiarrheal medications; electrolyte repletion (e.g., calcium and magnesium) to correct low electrolyte levels; thyroid replacement therapy for hypothyroidism; corticosteroid replacement for adrenalectomy; bisphosphonates, denosumab, and other medications for the treatment of

osteoporosis, prevention of skeletal-related events from bone metastases, and/or hypoparathyroidism; or adjuvant hormonal therapy for patients with a history of prostate cancer (e.g., gonadotropin-releasing hormone [GnRH] or luteinizing hormone-releasing hormone [LHRH] agonists) and breast cancer (e.g., GnRH/LHRH agonists, aromatase inhibitors, selective estrogen receptor modulators [SERMs] or degraders [SERDs]), that the patient has been on for the previous 28 days, are allowed, provided they are not on the list of prohibited concomitant medications (refer to Appendix 7).

Local treatment while receiving study treatment (e.g., palliative radiation therapy or surgery for bone metastases) may be permitted with sponsor approval (which may include confirmation of no PD by BICR); discussion with the Lilly medical team and documentation of approval is required. The disease site under consideration for palliative radiation or surgery must not be a target lesion for response assessment and must not be considered to be clinically or radiographically progressing. Lilly recommends holding selpercatinib for approximately 5 half-lives (approximately 7 days) before and after radiation therapy or surgery. Any concern for disease flare due to a prolonged period off of selpercatinib should be discussed with Lilly, who may permit holding selpercatinib for a shorter period of time.

Any herbal drugs, dietary supplements, etc. known to have anti-tumor activity are not permitted.

In addition, any disease progression requiring other forms of specific antitumor therapy will also necessitate discontinuation from the study.

Appropriate documentation for all forms of premedications, supportive care, and concomitant medications throughout the patient's participation in the trial must be captured on the case report form (CRF).

6.6. Dose Modification

Intolerable AEs that lead to treatment discontinuation (except alopecia) will meet criteria to be included in the TFFS endpoint. Intolerable AEs are defined as any study drug-related AE that meets protocol guidance for treatment discontinuation.

- Permanently discontinue treatment for any of:
  - Cabozantinib: development of visceral perforation or fistula formation, severe hemorrhage, serious arterial thromboembolic event (e.g., myocardial infarction, cerebral infarction), nephrotic syndrome, malignant hypertension, hypertensive crisis, persistent uncontrolled hypertension despite optimal medical management, osteonecrosis of the jaw, reversible posterior leukoencephalopathy syndrome
  - Vandetanib: development of prolonged QT interval not improved with electrolyte correction and/or dose reduction, severe skin reactions, ILD, ischemic cerebrovascular events, hemorrhage, heart failure, persistent uncontrolled hypertension despite optimal medical management, or reversible posterior leukoencephalopathy syndrome
  - Selpercatinib: malignant hypertension, hypertensive crisis, persistent uncontrolled hypertension despite optimal medical management, or severe/life-threatening hemorrhage. Patients with clinical benefit who experience recurrent hypersensitivity reaction or recurrent AST or ALT increase despite dose reductions should be

discussed with the Lilly medical team and may be allowed to continue treatment with more than 2 dose reductions if continuation is considered to be safe and in their best interest

Dose reductions should be made according to the following parameters using the dose reduction table below. Interrupt dosing for CTCAE v5.0 Grade 3 or greater AEs or Grade 2 AEs not resolved within 48 hours with appropriate supportive care (e.g., nausea not improved with antiemetics) and considered intolerable by the patient or the investigator.

- For selpercatinib related hypersensitivity, liver function test abnormalities, thrombocytopenia, and hypertension, see dose adjustments below in Sections 6.6.1, 6.6.2, 6.6.3, and 6.6.4, respectively.
- Regardless of treatment arm, study treatment may continue for hypertension that is considered Grade 3 on the basis of requiring ≥2 anti-hypertensives or more intensive anti-hypertensive therapy than baseline once blood pressure is stabilized.
- Dose modifications for ECG changes are described in Section 8.2.1. If a patient receiving selpercatinib or cabozantinib experiences QTCF >500 msec despite 2 dose reductions and if the investigator deems it in the best interest of the patient, the patient may continue treatment with study drug with Lilly medical approval. In addition, Lilly will request a copy of the ECGs for adjudication.
- Upon resolution (or return to patient's baseline) of AEs at least possibly related to treatment, reduce the dose as follows:
  - If previously receiving dose level 1, resume treatment at dose level -1
  - If previous receiving dose level -1, resume treatment at dose level -2
  - If previously receiving dose level -2, resume treatment at the same dose level. If a second AE requiring dose modification occurs at dose level -2, discontinue study treatment.
  - For AEs clearly unrelated to study treatment that resolve or return to patient's baseline in ≤14 days, dose reduction is not required.
  - Re-escalation to a prior dose level after a dose reduction is permitted once the AE requiring dose reduction is resolved. See Sections 6.6.1 through 6.6.4 and the IB for specific dose adjustments required for patients receiving selpercatinib.
  - Above are guidelines and may be superseded by local practice guidelines or advice per the local cabozantinib/vandetanib labels when appropriate.

Except as noted, a maximum of 2 dose level reductions will be allowed. Any patient requiring >42 days omission of treatment for drug-related toxicities will meet the criteria for study treatment discontinuation. Treatment omissions of >42 days in extenuating circumstances that are not drug-related (e.g. recovery from motor vehicle accident) may be approved by the Lilly medical team.

General Dose Reductions for Treatment Related Toxicities[a]

Dose Level	Time	Selpercatinib Dose (mg)	Cabozantinib Dose (mg)[b]	Vandetanib Dose (mg)
Dose Level 1	AM	160	140	300
	PM	160	-	-
Dose Level -1	AM	120	100	200
	PM	120	-	-
Dose Level -2	AM	80	60	100
	PM	80	-	-

[a] Unless other specific dose reductions, as per Sections 6.6.1, 6.6.2, 6.6.3, and 6.6.4.

In the instance that vandetanib 100-mg tablets are unavailable, but vandetanib 300-mg tablets are available, the below table is to be followed in adult patients.

Vandetanib Dose Modification using 300-mg Tablets for Adult Patients

Dose Level of Vandetanib	Vandetanib 300-mg tablets[a]
Dose Level 1	1 tablet QD every day
Dose Level -1[b]	1 tablet QD for 2 days, every 3 days
Dose Level -2[b]	1 tablet QD for 1 day, every 3 days

Abbreviations: QD = once daily.

[a] A starting dose of vandetanib should be 200 mg in adult patients with moderate renal impairment (creatinine clearance results between 30 and 50 mL/min).

[b] These dose regimens are expected to give similar reduced exposure corresponding to dose levels -1 and -2 in the standard dose modification table (General Dose Reductions for Treatment Related Toxicities).

Selpercatinib General Dose Reductions for Treatment Related Toxicities for Adolescent Patients

The dose (regardless of BSA calculation) should be no higher than the corresponding adult level for dose adjustments (e.g. Dose Level -1, 120 mg and Dose Level -2, 80 mg). Please see the table in Section 6.1.2 for selpercatinib dose rounding.

Dose Level	Time	Selpercatinib Dose (mg/m^2)
Dose Level 1	AM	92
	PM	92
Dose Level -1	AM	70
	PM	70
Dose Level -2	AM	46
	PM	46

Vandetanib General Dose Reductions for Treatment Related Toxicities and Starting Dose for Moderate Renal Impairment for Adolescent Participants

BSA (m^2)	Dose Reduction (mg)[a] or Starting Dose with Moderate Renal Impairment
0.7 - <0.9	-
0.9 - <1.2	100 QOD
1.2 - <1.6	100 QD
≥1.6	7 day schedule: 100-200-100-200-100-200-100

Abbreviations: BSA = body surface area; QD = once daily; QOD = once every other day.

a Participants with an adverse reaction requiring a dose reduction should stop taking vandetanib for at least a week. Dosing can be resumed at a reduced dose thereafter upon resolution or return to patient's baseline.

See Section 8.2.1 for additional information on dose reduction related to prolonged QTc.

Cabozantinib General Dose Reductions for Treatment Related Toxicities for Adolescent Participants

BSA (m^2)	Weekly Dose/Schedule for 1st Dose Reduction due to Toxicity	Weekly Dose/Schedule for 2nd Dose Reduction due to Toxicity
0.35 – 0.39	60 mg = 20 mg M, W, F	Off therapy
0.40 – 0.45	80 mg = 20 mg M, W, F, Sun	60 mg = 20 mg M, W, F
0.46 – 0.55	100 mg = 20 mg M, W, Th, Sat, Sun	60 mg = 20 mg M, W, F

BSA (m^2)	Weekly Dose/Schedule for 1st Dose Reduction due to Toxicity	Weekly Dose/Schedule for 2nd Dose Reduction due to Toxicity
0.56 – 0.64	120 mg = 20 mg M, T, W, F, Sat, Sun	80 mg = 20 mg M, W, F, Sun
0.65 – 0.78	140 mg = 20 mg QD	100 mg = 20 mg M, W, Th, Sat, Sun
0.79 – 0.90	160 mg = 40 mg M, W, F, Sun	120 mg = 20 mg M, T, W, F, Sat, Sun
0.91 – 1.09	200 mg = 40 mg M, W, Th, Sat, Sun	140 mg = 20 mg QD
1.10 – 1.17	200 mg = 40 mg M, W, Th, Sat, Sun	140 mg = 20 mg QD
1.18 – 1.36	240 mg = 40 mg M, T, W, F, Sat, Sun	160 mg = 40 mg M, W, F, Sun
1.37 – 1.65	300 mg = 60 mg M, W, Th, Sat, Sun	200 mg = 40 mg M, W, Th, Sat, Sun
1.66 – 1.85	360 mg = 60 mg M, T, W, F, Sat, Sun	240 mg = 40 mg M, T, W, F, Sat, Sun
1.86 – 2.07	420 mg = 60 mg Daily	300 mg = 60 mg M, W, Th, Sat, Sun
≥ 2.08	420 mg = 60 mg Daily	300 mg = 60 mg M, W, Th, Sat, Sun

Abbreviations: BSA = body surface area; QD = once daily.

6.6.1. Dose Modifications for Selpercatinib Hypersensitivity

If selpercatinib drug hypersensitivity is suspected, study drug should be held and treatment with steroids at 1 mg/kg prednisone (or equivalent) should be initiated. Upon resolution, selpercatinib may be resumed at a reduced dose of 40 mg BID (or adolescent equivalent dose) while continuing steroids at the same dose. Note that this dose reduction does not require sponsor approval. Hypersensitivity has recurred in some patients, typically at 3 to 6 hours following drug administration.

Discontinue selpercatinib for recurrent clinically significant hypersensitivity. In the absence of clinically significant recurrent drug hypersensitivity, the dose of selpercatinib may be escalated sequentially to 80 mg BID, 120 mg BID, and 160 mg BID (or adolescent equivalent doses) for a minimum of 7 days at each dose. Once the patient has tolerated treatment for a minimum of 7 days at the final dose, steroids may be tapered slowly.

6.6.2. Dose Modifications for Selpercatinib Related Liver Test Abnormalities

If a patient experiences Grade ≥3 elevated hepatic lab increases (ALT, AST, or direct bilirubin), study drug should be held and evaluation for potential alternative causes should be conducted (e.g., history of other hepatotoxic medications/substances, viral serologies, liver imaging). The grading is according to Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 with slight modification as described in Section 8.3. A repeat value 3 to 5 days after the initial finding of elevation of labs should be obtained to confirm the abnormality and to confirm if it is increasing or decreasing. Thereafter, hepatic labs should be monitored at least weekly until resolution to normal/baseline (depending on the clinical situation, resolution to Grade 1 if baseline is normal may be acceptable but awaiting normalization is preferable. If the abnormalities do not begin to resolve (or worsen) within 5 days of the AE, a hepatology consultation should be considered to evaluate the need for a liver biopsy. Due to the question of a

possible immune component to the lab abnormalities observed, some patients with persistent increases have initiated treatment with steroids, with subsequent improvement.

Upon resolution, selpercatinib may be resumed at a reduced dose of 2 dose levels lower than at which the abnormalities occurred with weekly lab monitoring. In the absence of recurrent abnormalities, the dose of selpercatinib may be escalated sequentially to the next higher dose level after a minimum of 2 weeks at the lowest dose level, and again to the dose level at which the abnormalities occurred after a minimum of 4 weeks at the dose level below which the abnormalities occurred. Once the patient has been treated at a stable dose of selpercatinib for a minimum of 4 weeks without recurrent lab abnormalities, the frequency of monitoring may be decreased (e.g., every 2 weeks for 2 months and then monthly thereafter). For patients who experience Grade ≥3 elevated hepatic labs on a dose of 80 mg BID (or adolescent equivalent dose), the Lilly medical team should be contacted for additional guidance to determine if continuation with dose modification is acceptable. If the patient experiences ≥Grade 3 elevated ALT, AST, or direct bilirubin at a dose of 40 mg BID, selpercatinib should be discontinued.

Please refer to Section 8.2.2. for additional monitoring that may need to be initiated.

6.6.3. Dose Modifications for Thrombocytopenia

If a patient is discovered to have thrombocytopenia Grade ≥3, study drug should be held and the patient should be evaluated for alternative causes (medications/substances, viral studies). A hematology consultation may be considered, as necessary, to understand the etiology and to consider a role for concomitant steroid therapy. The patient should undergo weekly CBC testing until the event has recovered to normal/baseline. Upon recovery to Grade 1 or better, the patient should resume selpercatinib at a reduced dose of one dose level reduction (if thrombocytopenia is determined to be related to selpercatinib) with weekly CBC surveillance for 1 full cycle.

6.6.4. Dose Modifications for Hypertension

For the purpose of the study, hypertension is defined as

- a sustained increase in blood pressure from baseline, as evidenced by ≥2 readings on ≥2 separate occasions, or
- a clinically significant elevation requiring acute treatment.

If hypertension occurs, study drug may be interrupted at the discretion of the investigator while

- a new anti-hypertensive medication regimen is initiated, or
- a pre-existing regimen is optimized to a reproducible reading of ≤140/90 mmHg.

If study drug is interrupted, it may be resumed at the same or a lower dose at the discretion of the investigator. In all cases, the patient should continue to undergo regular blood pressure monitoring to ensure adequate blood pressure control.

6.6.5. Dose Modification for Selpercatinib Interstitial Lung Disease/Pneumonitis

For Grade 2, withhold selpercatinib until resolution. Resume at next lower dose. Discontinue selpercatinib for recurrent ILD/pneumonitis.

For Grade 3 or 4, discontinue selpercatinib.

6.7. Intervention after the End of the Study

The end of study definition is defined in Section 4.4. Investigators will follow the schedule of activities provided in Section 1.3 until notified by Lilly that end of study has occurred.

6.7.1. Treatment after Study Completion

Study completion occurs after the clinical trial database is locked and final analysis of primary and secondary endpoints has been performed. Investigators will continue to follow SoAs (Section 1.3) for all patients until notified by Lilly that study completion has occurred.

6.7.1.1. Continued Access

Participants who are still on study intervention at the time of study completion may continue to receive study intervention if they are experiencing clinical benefit and no undue risks.

The continued access period will apply to this study only if at least 1 participant is still on study treatment when study completion occurs. Lilly will notify investigators when the continued access period begins.

Participants are not required to sign a new ICF before treatment is provided during the continued access period; the initial ICF for this study includes continued access under this protocol.

The participant's continued access to study intervention will end when a criterion for discontinuation is met (Section 7). Continued access follow-up will begin when the participant and the investigator agree to discontinue study intervention and lasts approximately 30 days. Follow-up procedures will be performed as shown in the Continued Access Schedule of Activities.

Participants who are in short-term follow-up when the continued access period begins will continue in short-term follow-up until the 30-day short-term follow-up visit is completed. Long-term follow-up does not apply.

Participants who are in long-term follow-up when the continued access period begins will be discontinued from long-term follow-up.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1. Discontinuation of Study Intervention

Possible reasons leading to permanent discontinuation of investigational product:

- **Subject Decision**
  - the participant or the participant's designee, for example, parents or legal guardian requests to discontinue investigational product.

If a clinically significant finding is identified 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.

In addition, participants will be discontinued from the investigational product in the following circumstances:

- the patient becomes pregnant during the study. See Section 8.3 regarding regulatory reporting requirements on fetal outcome.
- the patient is significantly noncompliant with study procedures and/or treatment
- disease progression (radiographic or clinical progression). Patients with disease progression per investigator assessment may continue treatment while awaiting BICR confirmation of progression. Exceptions for continuing study treatment beyond suspected radiographic progression may be made on a case-by-case basis for patients who are believed to be clinically benefiting from study treatment, and the investigator and Lilly medical team agree that continuing study treatment is in the patient's best interest. Expectations for required study procedures and data collection for each patient will be made at the time of approval.
- the patient experiences unacceptable toxicity from study treatment
- the patient, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication. Discontinuation from study treatment will occur prior to introduction of the new agent
- the investigator decides that the patient should be discontinued from study treatment.

Participants discontinuing from the investigational product for any reason should complete AE and other follow-up procedures, including imaging assessments, per Section 1.3 (Schedule of Activities), Section 8.3 (Adverse Events and Serious Adverse Events), and Section 8.2 (Safety Assessments) of the protocol.

Participants assigned to treatment Arm B who experience progression may cross-over to selpercatinib after meeting criteria in Section 5.2.1 and comply with procedures noted in Section 1.3.

7.2. Participant Discontinuation/Withdrawal from the Study

Participants will be discontinued in the following circumstances:

- 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
- participation in the study needs to be stopped for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and Good Clinical Practices (GCP)
- subject decision
    - the participant or the patient's designee, for example, parents or legal guardian] requests to be withdrawn from the study.

Participants discontinuing from the study prematurely for any reason should complete AE and other safety follow-up per Section 1.3 (Schedule of Activities), Section 8.3 (Adverse Events and Serious Adverse Events), and Section 8.2 (Safety Assessments) of this protocol.

Participants discontinuing from study procedures may continue to be followed for survival, as long as they have not withdrawn consent for follow-up. If an in-person visit is not possible, survival status may be obtained by the site by contacting the patient directly via phone.

7.2.1. Discontinuation of Inadvertently Enrolled Patients

If the sponsor or investigator identify a participant who did not meet enrollment criteria and was inadvertently enrolled, then the patient should be discontinued from study treatment unless there are extenuating circumstances that make it medically necessary for the patient to continue on study treatment. If the investigator and the sponsor agree it is medically appropriate to continue, the investigator must obtain documented approval from the sponsor 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 8.3 (Adverse Events and Serious Adverse Events), and Section 8.2 (Safety Assessments) of the protocol.

For sites located in the United Kingdom (UK) and Germany, refer to Appendix 5 for country-specific discontinuation guidelines.

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.

Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomized, including those who did not get investigational product. Public sources may be searched for vital status information, subject to local regulations. If vital status is determined, this will be documented and the participant will not be considered lost to follow-up.

Lilly personnel will not be involved in any attempts to collect vital status information.

Discontinuation of specific sites or of the study as a whole are handled as part of Section 10.1.8.

8. Study Assessments and Procedures

Unless otherwise stated in the subsections below, all samples collected for specified laboratory tests will be destroyed within 60 days of receipt of confirmed test results. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.

- 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 by the investigator 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.
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.
- Additional safety assessments (for example, ECG and labs) may be performed at investigator's discretion.

8.1. Efficacy Assessments

8.1.1. Imaging

Efficacy assessments include tumor evaluation every 8 weeks after treatment initiation through week 24, and then every 12 weeks thereafter as noted in the SoA. Images are to be submitted for BICR evaluation within 5 days of completion. Patients who discontinue treatment without radiographic progression by BICR should continue to be assessed per the above schedule until radiographic disease progression is confirmed by BICR or death.

All patients are required to undergo neck, chest, abdomen, and pelvis imaging at baseline and subsequent serial imaging at disease assessment time points. All images will be collected at a central facility for central reviewer assessment during the study. Response will be assessed per RECIST 1.1 requirements (Eisenhauer et al., 2009).

Finally, all patients will enter Long-Term Follow-Up (LTFU) for confirming disease progression (if not occurring on treatment), subsequent anticancer therapy(ies), and survival.

Baseline disease assessment with radiographic tumor measurements using computed tomography (CT) or magnetic resonance imaging (MRI) of neck, chest, abdomen, and pelvis or any other areas with suspected disease involvement must be completed within 28 days of C1D1. MRI with contrast is the preferred imaging modality for imaging the abdomen and pelvis of subjects with

MTC given the inherent challenges in RECIST 1.1 assessment of MTC liver metastases. If MRI is not obtainable, triple phase CT of the abdomen (nonenhanced, arterial phase, and portal venous phase imaging) with pelvis is recommended. Routine single-phase CT of the abdomen and pelvis in the portal venous phase if the recommendations listed above are not obtainable. Brain imaging is required at baseline only for patients with a history of CNS metastases, or if clinically indicated and subsequent serial scans are required if brain metastases are present at baseline (MRI preferred, CT with contrast is acceptable if MRI contraindicated). Bone imaging is required at baseline only for patients with known bone metastases or if clinically indicated, and subsequent serial scans are required if bone metastases are present at baseline (MRI or CT with bone windows preferred).

For each modality, IV and oral contrast should be utilized (chest CT does not require contrast) unless there is a clear contraindication (e.g., decreased renal function or allergy that cannot be addressed with standard prophylactic treatments). Post-baseline imaging should be performed every 8 weeks (±7 days) for 24 weeks and every 12 weeks (±7 days) thereafter, including imaging of the neck, chest, abdomen, and pelvis, and any other known sites of disease, using the same modality(ies) as used for baseline imaging obtained during the screening period until PD, withdrawal of consent, or death. For the purpose of determining progression for eligibility, a change in modality *may* be acceptable if clear progression can be confirmed by central review, especially when a less sensitive modality was used for the second scan (e.g., liver metastases present on CT abdomen occurring after a previously normal MRI abdomen). Additional studies can also be performed at any time as clinically indicated. Please see the Site Imaging Manual for guidelines on how the various imaging studies should be performed and transmitted for central review.

For patients who progress on study treatment and begin a different anti-cancer therapy (including patients who are initially assigned to the control arm and crossover to receive selpercatinib), PFS2 will be collected. It is recommended to maintain the study imaging schedule in patients who have discontinued treatment; that is, to continue imaging every 8 weeks for the first 24 weeks of the next therapy, then every 12 weeks, as much as allowed according to the patient's new treatment standard of care. These images will be collected centrally and the overall tumor assessment should be entered into the CRF.

8.1.2. BICR Assessment

Response assessments, including verification of PR or CR and disease progression will be assessed by BICR. These data will constitute the primary assessment for PFS and best overall response (BOR) analyses. The BICR will conduct assessment of tumor response by RECIST 1.1.

Following each scan, the investigator will assess for progression using RECIST 1.1 and submit the scan for BICR review as outlined in Section 1.3. The table below outlines the potential actions following BICR review of imaging.

Investigator assessment	BICR assessment	Actions
Progressive Disease[a]	Progression verified	• Discontinue study treatment **OR** • Continue study treatment with sponsor approval if the patient is believed to be clinically benefitting **OR** • Crossover to selpercatinib (only patients progressing on Arm B are eligible for crossover)
	Progression not verified	• Continue on study treatment if the patient is believed to be clinically benefitting until a criterion for discontinuation is met **OR** • Discontinue study treatment; imaging and submission for central review should continue until 1. radiographic disease is verified by the BICR, 2. death, 3. withdrawal of consent, or 4. study completion. Patients on Arm B would be eligible to cross over upon BICR documentation of progression.
Non-progression	In the case of investigator-assessed non-progression, results are not reported back to investigator as BICR assessment is only used for endpoint assessment.	• Continue on study treatment until progressive disease or another criterion for discontinuation is met

[a] For patients where the investigator assessment is PD, it is at the discretion of the investigator if study treatment is continued until the BICR assessment is received.

In the crossover period scans will be collected and stored for future review, if needed.

8.2. Safety Assessments

For each patient, AEs, ECGs, vital signs, laboratory tests, and other tests should be collected as shown in the SoA (Section 1.3).

Results from any clinical laboratory test analyzed by a central laboratory (refer to Section 10.2) will be provided to investigative sites by Lilly or its designee.

Refer to Section 8.3 for details on the recording of AEs.

Lilly will periodically review evolving aggregate safety data within the study by appropriate methods.

Planned time points for all safety assessments are provided in the SoA.

Tanner staging (Marshall and Tanner 1969, Marshall and Tanner 1970) is required for any patient under age 18 (until sexual maturity is reached) in order to monitor the development of adolescent patients treated with selpercatinib.

Participants who have not yet obtained full adult height will undergo MRI of one knee at baseline and every 6 months while the growth plate remains patent. Right knee is preferred, but whichever knee is imaged at baseline should be imaged at all time points.

Adolescents who have had a documented growth rate of <1 cm/year over the prior 2 years and/or have reached a midparental height of over 152 cm in girls and 167 cm in boys, are likely to have obtained full adult height. If it is unclear that a patient has obtained full adult height, pretreatment tibial radiographs (AP and lateral views) of the right knee should be obtained and MRI performed only if the growth plate remains patent. If the growth plate remains patent, the patient will have a MRI performed every 6 months until the growth plate is no longer patent.

In addition, a Safety Follow-up (SFU) visit 28 days (±7 days) after the last dose of selpercatinib, cabozantinib, or vandetanib will occur to determine the status of unresolved AEs.

8.2.1. Electrocardiograms

- ECG monitoring should be performed as outlined in the SoA (Section 1.3). QTcF values should be recorded on the CRF. In addition, Lilly may request a copy of the ECGs for adjudication.

The actions below should be taken if the QTcF is greater than 500 msec on at least 2 of 3 ECGs (i.e., Grade 3 prolongation per CTCAE) and the triplicate average QTcF is greater than 500 msec OR is >60 msec longer than baseline QTcF:

- Manually review to confirm accuracy. ECGs will be interpreted by a qualified physician (the investigator or qualified designee) at the site for immediate patient management.
- Assess for alternative causes (concomitant medications, electrolyte abnormalities, presence of pacemaker). Clinical chemistry should be assessed and if electrolytes are abnormal, they should be repleted as indicated. Potassium should be ≥4 meq/L and less than the upper limit of normal (ULN) and magnesium and calcium should be within normal limits. Dose adjustment is not required if an alternative cause is found and if, in the medical judgment of the investigator, the patient is able to safely continue study treatment at his/her current dose while the cause of QTc change is being addressed.
- Institutional guidelines or standard of care measures for management of QTcF interval >500 msec and/or associated arrhythmias should be initiated.
- If the patient is on Arm A, selpercatinib should be reduced at least 1 dose level.
- If the patient is on Arm B1 (cabozantinib), dose adjustments should occur per label/institutional guidelines.
- If the patient is on Arm B2 (vandetanib), treatment should be held until QTcF returns to <450 msec, then reduce vandetanib by 1 dose level. If a further event of CTCAE Grade 3 or higher toxicity or prolongation of the ECG QTc interval occurs, dosing with vandetanib should be permanently stopped. The patient must be monitored appropriately.

Fridericia's QT Correction Formula

Formula	**Fridericia** **$QTcF = QT / (RR)^{1/3}$**

Abbreviations: QT = ECG interval measured from the onset of the QRS complex to the offset of the T wave; QTcF = QT interval corrected for heart rate using Fridericia's formula; RR = time between corresponding points on 2 consecutive R waves on ECG.

8.2.2. Clinical Safety Laboratory Assessments

- Investigator sites should use local laboratories to determine patient eligibility and treatment decisions.
    - See Appendix 2 for the list of clinical laboratory tests to be performed and Section 1.3 (SoA) for the timing and frequency.
- All laboratory tests, with the exception of tumor markers, with values considered clinically significantly abnormal during participation in the study or until completion of V801 should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or Lilly medical team.
    - If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
    - All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.

8.2.2.1. Hepatic Safety Monitoring

In study participants with baseline ALT/AST <1.5X ULN

If a study participant enrolled with baseline ALT/AST <1.5X ULN experiences elevated ALT/AST ≥3X ULN and elevated TBL ≥2X ULN, or ALT/AST ≥5X ULN liver testing (Appendix 4) including ALT, AST, TBL, direct bilirubin, gamma-glutamyl transferase, and creatine kinase should be repeated within 3 to 5 days to confirm the abnormality and to determine if it is increasing or decreasing. 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 study CRP/CRS. Monitoring of ALT, AST, and TBL should continue until levels normalize or return to approximate baseline levels.

In study participants with baseline ALT/AST ≥1.5X ULN

If a study participant enrolled with baseline ALT/AST ≥1.5X ULN experiences elevated ALT/AST ≥3X baseline or ALT/AST ≥2X baseline and TBL ≥2X ULN, liver testing (Appendix 4) including ALT, AST, TBL, direct bilirubin, gamma-glutamyl transferase, and creatine kinase should be repeated within 3 to 5 days to confirm the abnormality and to determine if it is increasing or decreasing. 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 study CRP/CRS. Monitoring of ALT, AST, and TBL should continue until levels normalize or return to approximate baseline levels.

Hepatic data (Appendix 4) should be collected in the event that 1 (or more) of the following conditions is met for the patient during the course of the study:

- In patients enrolled with baseline ALT/AST <1.5X ULN:
  a. Elevated ALT/AST ≥3X ULN and elevated total bilirubin ≥2X ULN
  b. ALT/AST ≥5X ULN on 2 consecutive tests.
- In patients enrolled with baseline ALT/AST ≥1.5X ULN (regardless of whether or not they have hepatic metastasis):
  a. Elevated ALT/AST ≥2X baseline and elevated TBL ≥2X ULN
  b. Elevated ALT/AST ≥3X baseline on 2 consecutive tests.
- All patients
  a. Discontinuation from study treatment due to a hepatic event or abnormality of liver tests
  b. Occurrence of a hepatic event considered to be a SAE.

8.2.2.2. Chylothorax and Chylous Ascites Monitoring

If a participant develops a pleural effusion or abdominal ascites or both while on selpercatinib, fluid sampling and testing should be considered as part of the management algorithm whenever possible. The etiology of this finding varies and distinguishing chylous fluid from malignant (as well as other causes such as infectious) may impact management significantly (for example, presumption of disease progression with premature discontinuation of therapy). Additionally, a diagnosis of chylous effusions or ascites or both may indicate a role for conservative measures such as fluid replacement, dietary alteration or medical therapy or both (for example, somatostatin analogue) prior to consideration of more invasive measures. Selpercatinib interruption and dose modification should follow the general strategy as outlined in Section 6.6 (Dose Modification), based upon severity of the event.

8.2.2.3. Renal Safety Monitoring

In vitro, selpercatinib is an inhibitor of the drug transporter MATE1 and may reduce the clearance of MATE1 substrates (for example, creatinine). Selpercatinib may increase serum creatinine due to inhibition of the renal tubular secretion transporter MATE1, without affecting glomerular function. Complementary markers such as blood urea nitrogen (BUN), cystatin C, or calculated glomerular filtration rate (GFR), which are not based on creatinine, may be considered to determine whether renal function is impaired.

8.2.2.4. Thyroid Function Monitoring

Hypothyroidism was reported in patients receiving selpercatinib in clinical trials. Monitor patients for hypothyroidism and treat as medically appropriate. Baseline laboratory measurement of thyroid function is recommended in all patients. Patients with preexisting hypothyroidism should be treated as per standard medical practice prior to the start of selpercatinib treatment. All

patients should be observed closely for signs and symptoms of thyroid dysfunction during selpercatinib treatment. Thyroid function should be monitored periodically throughout treatment with selpercatinib. Patients who develop thyroid dysfunction should be treated as per standard medical practice. However, patients could have an insufficient response to substitution with levothyroxine (T4), as selpercatinib may inhibit the conversion of levothyroxine to liothyronine (T3) and supplementation with liothyronine may be needed.

8.3. Adverse Events and Serious Adverse Events

The investigator should provide AE verbatim terms and then the terms will be mapped by Lilly or its designee to corresponding terminology within the Medical Dictionary for Regulatory Activities (MedDRA) Lower Level term (LLT) dictionary. The investigator will use Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 to assign AE severity grades. Lilly recommends a slight modification when implementing the CTCAE V5.0. Post baseline grading for all laboratory values should be done per normal limit references, where specified, regardless of whether the assessment is normal or abnormal at baseline.

Investigators are responsible for monitoring the safety of participants who have entered this study and for alerting Lilly or its designee to any event that seems unusual, even if this event may be considered an unanticipated benefit to the participant.

The investigator is responsible for the appropriate medical care of participants during the study.

The investigator remains responsible for following, through an appropriate health care option, AEs that are serious or otherwise medically important, considered related to the investigational product or the study, or that caused the participant to discontinue the investigational product before completing the study. The participant should be followed until the event resolves, stabilizes with appropriate diagnostic evaluation, or is otherwise explained. The frequency of follow-up evaluations of the AE is left to the discretion of the investigator.

Lack of drug effect is not an AE in clinical studies, because the purpose of the clinical study is to establish treatment effect.

After the ICF is signed, study site personnel will record via CRF the occurrence and nature of each participant's pre-existing conditions, including clinically significant signs and symptoms of the disease under treatment in the study. In addition, site personnel will record any change in the condition(s) and any new conditions as AEs. Investigators should record their assessment of the potential relatedness of each AE to protocol procedure, investigational product, via CRF.

The investigator will interpret and document whether or not an AE has a reasonable possibility of being related to study treatment, study device, or a study procedure, taking into account the disease, concomitant treatment or pathologies.

A "reasonable possibility" means that there is a cause and effect relationship between the investigational product, study device and/or study procedure and the AE.

The investigator answers yes/no when making this assessment.

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 AEs.

Planned surgeries and nonsurgical interventions should not be reported as AEs unless the underlying medical condition has worsened during the course of the study.

If a participant's investigational product is discontinued as a result of an AE, study site personnel must report this to Lilly or its designee via CRF, clarifying if possible, the circumstances leading to any dosage modifications, or discontinuations of treatment. Dose modifications and treatment discontinuation due to an AE should follow criteria defined in Section 6.6 (Dose Modifications). An independent review committee will review blinded data to determine which treatment discontinuations due to an AE meet the treatment failure event criteria for the primary analysis.

Only AEs reasonably possibly related to study procedures should be recorded in the eCRF, after signing the prescreening ICF. If an SAE occurs after signing the pre-screen ICF, the SAE should be reported to the sponsor as per SAE reporting requirements and timelines if it is considered reasonably possibly related to study procedures.

All AEs occurring after signing the main study ICF are recorded in the eCRF and assessed for serious criteria. The SAE reporting to the sponsor begins after the patient has signed the main study ICF and has received investigational product. However, if an SAE occurs after signing the main Study ICF, but prior to receiving investigational product, the SAE should be reported to the sponsor as per SAE reporting requirements and timelines if it is considered possibly related to study procedures.

Adverse events

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

Events meeting the AE definition

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

- Medication error, misuse, or abuse of IMP, including signs, symptoms, or clinical sequelae.
- Lack of efficacy or failure of expected pharmacological action per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events NOT meeting the AE definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- The disease or disorder being studied or expected progression, signs, or symptoms of the disease or disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure, for example, endoscopy, appendectomy. The condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Serious Adverse Events

An SAE is any AE from this study that results in one of the following outcomes:

- death
- initial or prolonged inpatient hospitalization
- a life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

All AEs occurring after signing the ICF are recorded in the CRF and assessed for serious criteria. The SAE reporting to the sponsor begins after the participant has signed the ICF and has received investigational product. However, if an SAE occurs after signing the ICF, but prior to receiving investigational product, the SAE should be reported to the sponsor as per SAE reporting requirements and timelines (see Section 8.3.1) only if it is considered reasonably possibly related to study procedure.

Serious adverse events, including death, caused by disease progression should not be reported unless the investigator deems them to be possibly related to study treatment. Study site personnel must alert Lilly 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. Participants with a serious hepatic adverse event should have additional data collected using the CRF.

Pregnancy (during 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 to collect data on the outcome for both mother and fetus.

Investigators are not obligated to actively seek AEs or SAEs in subjects once they have discontinued and/or completed the study (the participant disposition CRF has been completed). However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably possibly related to the study treatment or study participation, the investigator must promptly notify Lilly.

Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the IB and that the investigator identifies as related to investigational product or procedure. United States 21 CFR 312.32 and European Union Clinical Trial Directive 2001/20/EC and the associated detailed guidances or national regulatory requirements in participating countries require the reporting of SUSARs. Lilly has procedures that will be followed for the identification, recording and expedited reporting of SUSARs that are consistent with global regulations and the associated detailed guidances.

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

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

8.3.2. 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).

8.3.3. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will evaluate the reported SAEs, including confirmation of relatedness and assessment of expectedness. The sponsor has processes for safety reports

for identification, recording, and expedited reporting of SUSARs according to local regulatory requirements. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.

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

8.3.4. 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 completion of V801.
- 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 3.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.
- Additional requirements for pregnancy testing during and after study intervention are located in Appendix 3.
- The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

8.3.5. Cardiovascular and Death Events

Not applicable.

8.3.6. Complaint Handling

Lilly 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.

8.4. Treatment of Overdose

Refer to the IB and/or product label for selpercatinib, cabozantinib, or vandetanib for available information on the signs, symptoms, and treatment of overdose.

8.5. Pharmacokinetics

At the visits and times specified in the SoA (Section 1.3), blood samples will be collected to determine the plasma concentrations of selpercatinib.

A maximum of 5 samples may be collected at additional time points during the study if warranted and agreed upon between both the investigator and sponsor. Instructions for the collection and handling of blood samples will be provided by the sponsor. The actual date and time [24-hour clock time] of each sampling and prior dose will be recorded.

Blood for PK assessment will be collected on C1D8, and at first day of each consecutive cycle up to Cycle 6 and should be collected regardless even if study drug will be held for the next cycle. Samples are to be drawn within [redacted] hours prior to dose, and exact time of sample collection should be recorded. In addition, time of previous dose should be recorded. Additional PK may also be assessed in patients when considered necessary by the Investigator to understand exposure in relationship to possible safety. Additional samples should be considered for patients experiencing selpercatinib-related drug hypersensitivity at onset of event, and at resolution of event.

Bioanalytical samples collected to measure investigational product concentration and metabolism and/or protein binding will be retained for a maximum of 2 years following last participant visit for the study. During this time, samples remaining after the bioanalyses may be used for exploratory analyses, such as metabolism, transport and/or protein binding work.

8.6. Pharmacodynamics

Not applicable.

8.7. Genetics

8.7.1. Blood Samples for Pharmacogenetic Research

A blood sample will be collected for pharmacogenetic analysis as specified in the SoA (Section 1.3) where local regulations allow.

Samples will not be used to conduct unspecified disease or population genetic research either now or in the future. Samples will be used to investigate variable response to selpercatinib and to investigate genetic variants thought to play a role in MTC and to determine whether genetic alterations identified in tumor samples are somatic or germline variants. Assessment of variable response may include evaluation of AEs or differences in efficacy.

All samples will be coded with the patient number. These samples and any data generated can be linked back to the patient only by the investigator site personnel.

Samples will be retained at a facility selected by Lilly for a maximum of 15 years after the last participant visit for the study, or for a shorter period if local regulations and/or ethical review boards (ERBs)/ IRBs impose shorter time limits. This retention period enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in the development of selpercatinib or after selpercatinib becomes commercially available.

Molecular technologies are expected to improve during the 15-year storage period and therefore cannot be specifically named. However, existing approaches include whole genome or exome sequencing, genome wide association studies, and candidate gene studies. Regardless of technology utilized genotyping data generated will be used only for the specific research scope described in this section.

8.8. Biomarkers

8.8.1. Samples Required for Eligibility

Eligibility is dependent on having adequate tumor tissue for confirmatory central *RET* testing. Mandatory provision of an unstained, archived tumor tissue sample in a sufficient quantity to allow for retrospective central analysis of *RET* mutation status.

a) Tumor samples must be formalin fixed and paraffin embedded (FFPE). Blocks should be provided wherever possible, but unstained slides are also permitted. Acceptable sample collection methods include surgical resection (preferred) core biopsy, or FFPE fine needle aspiration. Biopsy samples taken from bone metastasis and cytology samples are unsuitable for testing and should not be provided. Sample may be collected from primary or metastatic tumor sites.
b) The investigator will be asked to provide
    a. FFPE tumor tissue blocks, or
    b. A minimum of 16 unstained slides from FFPE tissue block presented on slides. Preferably, each section should be approximately 5 µm thick. In certain circumstances, fewer slides may be acceptable, only with sponsor approval (i.e., where it can be demonstrated by the site that fewer slides will provide a sample in sufficient quantity for retrospective central analysis of *RET* alteration). Note that these slides are required in addition to any slides required prospectively to determine *RET* status for study eligibility.
    c. If it is considered safe to perform, patients who do not have sufficient available tumor tissue may undergo a fresh tumor biopsy to meet eligibility requirements.
    d. For patients who had eligibility determined by germline testing, the investigator should contact the sponsor to determine if a smaller amount of tissue is required.

Patients must agree to have any leftover tissue (tissue that remains after confirmatory *RET* testing) retained for the use of secondary studies outlined below and in Section 5.1, inclusion criterion 4a.

8.8.2. Biomarkers

Biomarker research is performed to address questions of relevance to drug disposition, target engagement, pharmacodynamics, mechanism of action, resistance mechanisms, variability of participant response (including safety), and clinical outcome. Sample collection is incorporated into clinical studies to enable examination of these questions through measurement of biomolecules including DNA, cfDNA, ribonucleic acid (RNA), proteins, lipids, and other cellular elements.

Archived tumor tissue will be obtained for patients, if available. Archived tumor tissue should be submitted, either via tumor block (preferred) or unstained slides. Lilly has a right to retain a portion of the submitted tissue. Archival blocks will be sectioned and returned to the study site. Slides and tissue samples collected on-study will not be returned. Patients who do not have sufficient archival tumor tissue available must undergo a fresh tumor biopsy, if it is considered safe to perform, prior to treatment. A tissue biopsy may be collected at the time of progression if

it can be safely performed. For biopsies performed in the setting of disease progression, please contact the sponsor to inform them of the planned biopsy. Samples collected will be utilized for retrospective concordance of one or more companion diagnostic tests.

Blood and tissue samples for biomarker research will be collected at the times specified in the SoA (Section 1.3), where local regulations allow. Whole blood will be collected to characterize *RET* mutations and concurrently activated oncogenic pathways in cfDNA and to compare *RET* mutation status in tumor and cfDNA samples. It is possible that biomarker data for patients in the study has already been generated from samples that were collected and analyzed prior to enrolling in this study. This may include pathology reports and data generated from genetic analyses. If available, these data may be requested from medical records for use in the research described in Sections 8.7 and 8.8. Patients must have a *RET* alteration as outlined in Section 5.1. For all patients, a redacted Molecular Pathology Report or other report(s) describing tumor or germline *RET* mutations should be submitted to the sponsor, designee, or central laboratory. In regions or at sites where *RET* is not standard of care and/or an acceptable local test (as defined by Lilly) is not available, a pre-screening consent will be used to provide information to the patient regarding testing to determine tumor *RET* status. The results of the initial or retrospective concordance testing will include other genes in addition to *RET*.

Samples will be used for research on the drug target, disease process, variable response to selpercatinib, pathways associated with MTC and the mechanism of action of selpercatinib. These samples may also be used to develop research methods or in validating diagnostic tools or assays.

All samples will be coded with the participant number. These samples and any data generated can be linked back to the participant only by the investigator site personnel.

Samples will be retained at a facility selected by Lilly for a maximum 15 years after the last participant visit for the study, or for a shorter period if local regulations and ERBs/IRBs impose shorter time limits. This retention period enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in the development of selpercatinib or after selpercatinib become commercially available. Technologies are expected to improve during the 15-year storage period and, therefore, cannot be specifically named. Existing approaches, including mutation profiling, copy number variability analysis, gene expression assays, multiplex assays, and/or immunohistochemistry may be performed on these tissue samples to assess potential associations between these biomarkers and clinical outcomes.

8.9. Medical Resource Utilization and Health Economics

8.9.1. Patient-reported Outcomes

Self-reported questionnaires will be administered according to the SoA (Section 1.3) in countries where the questionnaires have been translated into the native language of the region. Only patients age 18 or older who are literate in an available translation will complete the questionnaires. Since no paper version of the questionnaires is provided, patients with religious objection to using electronic devices are not required to complete these activities. Instruments that are completed daily will be collected for the first year of patient treatment then will be

discontinued; instruments that are collected weekly or less frequently will be continued for the full duration of patient treatment as described in the Schedule of Activities (Section 1.3).

8.9.2. Bristol Stool Form Scale and Bowel Movement Frequency

The Bristol Stool Form Scale is a single item that asks about worst stool form (Lewis and Heaton 1997). The bowel movement frequency is a single item that asks the participant to quantify the number of bowel movements in the past 24 hours. Patients will complete these items daily on the device provided; sites will not administer this instrument.

8.9.3. Worst Pain Numeric Rating Scale (NRS)

The Worst Pain Numeric Rating Scale (NRS) is a single item, subject-administered, 11-point horizontal scale anchored at 0 and 10, with 0 representing “no pain” and 10 representing “pain as bad as you can imagine.”

The recall period is the last 24 hours, and will be completed daily by the patient on the device provided; sites will not administer this instrument.

8.9.4. PRO-CTCAE

The PRO-CTCAE is a patient-reported outcome measurement system developed by the National Cancer Institute to collect symptomatic AEs from cancer patients enrolled in clinical trials (Basch et al. 2014; Dueck et al. 2015). These items have been developed to assess symptomatic AEs from the patient perspective associated with cancer therapy, to complement the CTCAE data collected at the site level (Basch et al. 2014, Atkinson et al. 2016). The information from the PRO-CTCAE will not be available to the patient or onsite clinicians for clinical patient management. Specific items were selected from the library that occurred in at least 24% of the study population receiving selpercatinib, cabozantinib or vandetanib; additionally, a minimum of the 5 most common side effects of each agent were also included (Schlumberger et al. 2017; Elisei et al. 2013; Wells et al. 2012; cabozantinib USPI 2016; cabozantinib SmPC 2016; vandetanib USPI 2014; vandetanib SmPC 2014). The PRO-CTCAE will be completed weekly by the patient via the device provided; sites will not administer this instrument.

8.9.5. FACT-GP5

This is a single item from the Functional Assessment of Cancer Therapy (FACT) general scale to assess overall side-effect burden (FACT-GP5). This item will be completed weekly by the patient via the device provided; sites will not administer this instrument.

8.9.6. HRQoL (EORTC QLQ-C30)

Health-related quality of life will be assessed with the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 Version 3.0 (EORTC QLQ-C30 [Aaronson et al. 1993]).

The EORTC QLQ-C30 self-reported general cancer instrument consists of 30 items covered by 1 of 3 dimensions:

- global health status/quality of life (2 items)

- functional scales (15 total items addressing either physical, role, emotional, cognitive, or social functioning)
- symptom scales (13 total items addressing either fatigue, nausea/vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, or financial impact).

Electronic versions of the questionnaires will be used and will be available to the patient on the provided device. The full scale will be completed electronically on day 1 of each cycle at the site, whereas the physical function items of this scale, item library 19 (EORTC IL19) will be completed weekly by the patient; sites will not administer this instrument.

8.9.7. Health Status (EQ-5D-5L)

Health status will be assessed using the EQ-5D-5L (Janssen et al. 2008). This utility measure is an important input for economic evaluations concerning the value of treatment interventions. Patients will complete the 5-dimension (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), 5-level (no problem, slight, moderate, severe, or extreme problem) assessment according to the SoA (Section 1.3). A unique EQ-5D health state is defined by combining 1 level from each of the 5 dimensions. Additionally, patients will indicate their current health status by marking on a visual analogue scale (VAS) ranging from 100 (best imaginable health state) to 0 (worst imaginable health state). The recall period is "today." The EQ-5D-5L is designed for self-completion by respondents and is cognitively simple, taking only a few minutes to complete, and will be administered electronically at the study site on Day 1 of each cycle of therapy. EQ-5D-5L responses may be incorporated into cost utility analyses, but will not be included in the clinical study report.

8.9.8. Healthcare Resource Utilization

Health care resource utilization will be collected in the CRF by the investigator and study-site personnel for all participants throughout the study. Protocol-mandated procedures, tests, and encounters are excluded.

The data collected will include:

- Hospitalization (Yes or no) and duration of hospitalization (admit and discharge dates)
- Emergency room visits (Yes or no) and dates
- Supportive care medications (G-CSF use, analgesics, transfusions)

Pain medication will be classified into medication categories, using the World Health Organization analgesic ladder. A medication category will be assigned based on the maximum analgesic therapy administered for that cycle on a routine basis.

9. Statistical Considerations

9.1. Statistical Hypotheses

Treatment of patients with progressive, advanced, kinase inhibitor-naïve, *RET*-mutant MTC with selpercatinib in the first line setting will provide a clinically meaningful increase in PFS over treatment with cabozantinib/vandetanib.

9.2. Sample Size Determination

An initial assumption of 74 PFS events at the final analysis provides approximately 80% power to detect a HR of 0.5 using the log-rank test and a 1-sided type I error of 2.5%. Given the historical data outlined in Section 4.2, a median PFS of 25 months is assumed for Arm B. HR of 0.5 corresponds to an improvement in median PFS from 25 months for Arm B to 50 months for Arm A. Approximately 250 patients will be enrolled based on these initial assumptions.

The sample size re-estimation will be based on the actual number of observed PFS events at the time of the pre-specified interim efficacy analysis, so the sample size adjustment has the purpose of modifying the number of events. The number of patients will be adjusted accordingly so that the required total number of events could be achieved in a desired timeframe.

Re-estimation of the number of PFS events will be conducted only once, during the pre-specified interim efficacy analysis, based on the unblinded comparative results observed at this analysis. Based on prespecified criteria described in the Adaptive Design Charter the following scenarios are possible:

- the study will be declared positive due to overwhelming efficacy
- the study will continue without change to the final analysis (i.e., the re-estimated total number of events will be equal to the initial planned total number of events)
- the re-estimated total number of events required for the final analysis will be determined and the study will continue to the final analysis.

The re-estimated total number of events could be increased from the initial assumption of 74 to a maximum of approximately 284 events to maintain the conditional power (conditional probability of a statistically significant treatment effect at the end of the trial) at a prespecified level. A maximum of 284 PFS events was selected based on the original protocol under a fixed study design to provide approximately 80% power to detect a HR of 0.7. The total number of patients could be increased from approximately 250 up to approximately 400. The total study duration will be capped at 6 years from the first patient visit regardless of actual number of events observed. A duration of 6 years is considered to be a relevant timeframe considering that the treatment landscape may change substantially and continuation on study follow-up may present an undue burden on participants. Details of adaptation decision rules are described in the Section 9.5 and the Adaptive Design Charter.

9.3. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Entered	All participants who sign informed consent for treatment
ITT/Enrolled	All randomized patients, even if a patient does not take the assigned treatment, does not receive the correct treatment, or otherwise does not follow the protocol. Patients will be analyzed according to the treatment group they were assigned to regardless of what actual treatment they receive.
Evaluable	Defined in specific subsections below, where applicable
Crossover	A subpopulation of patients included in the ITT population who were randomly assigned to Arm B, crossed over and took at least 1 dose of selpercatinib
Safety	All randomized participants who take at least 1 dose (including a partial dose) of study treatment. Analysis will be based on the actual treatment a participant received on the first study treatment administration, regardless of which treatment they were assigned to receive (“as treated”).
Tolerability Evaluable	All patients who were randomized prior to the interim efficacy analysis and received the first dose of study treatment at least 6 months prior to the data cutoff date. Analysis of tolerability will be based on the actual treatment a patient received on the first study treatment administration regardless of which treatment they were randomized to receive (“as treated”)

Abbreviations: ITT = Intent to treat.

9.4. Statistical Analyses

9.4.1. General Statistical Considerations

All efficacy analyses will be performed using the intention-to-treat (ITT) population, unless otherwise specified.

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

Efficacy analyses will be conducted on the ITT data set, as defined in Section 9.3. This set includes all randomized patients, according to the treatment arm to which they were assigned.

Safety analyses will be conducted on the safety data set, as defined in Section 9.3. This set includes all data from all participants who received at least 1 dose of the study drug according to the treatment the participants actually received.

All tests of treatment effects will be conducted at a 2-sided alpha level of 0.05 (or equivalently 1-sided alpha level of 2.5%), as appropriate, unless otherwise stated.

Any change to the data analysis methods described in the protocol will require an amendment ONLY if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the clinical study report (CSR). Additional exploratory analyses of the data will be conducted as deemed appropriate.

Handling of missing, unused, and/or spurious data is addressed prospectively in the overall statistical methods described in the protocol, and/or in the SAP, where appropriate. Adjustments to the planned analyses are described in the final CSR.

9.4.2. Treatment Group Comparability

9.4.2.1. Participant Disposition

A detailed description of patient disposition will be provided according to CONSORT publishing requirements, including a summary of the number and percentage of patients entered into the study, enrolled in the study, and treated, as well as number and percentage of patients completing the study (patients who receive ≥1 dose of study drug and have ≥1 postbaseline tumor assessment), or discontinuing (overall and by reason for discontinuation). A summary of all important protocol deviations will be provided.

9.4.2.2. Participant Characteristics

Demographic data are collected and reported to demonstrate that the study population represents the target patient population.

A summary of baseline patient and disease characteristics, historical diagnoses, pre-existing conditions, and prior therapies will be reported by arm and stage using descriptive statistics. Other patient baseline characteristics will be summarized as deemed appropriate.

9.4.2.3. Concomitant Therapy

A summary of concomitant medications and transfusions by arm and stage will be reported.

9.4.2.4. Treatment Compliance

Oral drug compliance will be assessed as the proportion of treatment that is actually taken, relative to what is expected, after accounting for protocol-defined dose adjustments. Study treatment taken will be derived from the difference between the total number of capsules/tablets dispensed and returned over the course of the patient's treatment. A patient will be considered noncompliant if he or she takes <75% or ≥125% of the planned doses.

9.4.2.5. Extent of Exposure

The duration on therapy, dose omissions, dose reductions, and dose intensity for each drug will be summarized for all treated patients by parts and arms.

9.4.2.6. Post-Study-Treatment Therapy

The numbers and percentages of patients receiving post-study-treatment anticancer therapies will be provided by type of therapy (surgery, radiotherapy, or systemic therapy), and by drug class and/or name, overall, and by line of therapy.

9.4.3. Efficacy Analyses

9.4.3.1. Primary Analyses

Progression-free survival confirmed (PFS) by BICR is defined as the time from randomization until the occurrence of documented disease progression by the BICR, per RECIST 1.1 criteria (Eisenhauer et al. 2009), or death from any cause in the absence of BICR-documented PD. Patients known to be alive and without disease progression will be censored at the time of the last adequate tumor assessment.

The BICR PFS will be compared between treatment arms using the Cui, Hung and Wang (CHW) testing procedure (Cui et al. 1999) to control the type I error at an overall 1-sided 2.5% significance level:

- At the interim efficacy analysis, the BICR PFS will be compared using a conventional stratified logrank test, stratified by the 2 randomization strata based on IWRS data: RET mutation (M918T vs. other) and intended control treatment (cabozantinib vs. vandetanib).
- At the final analysis, the BICR PFS will be compared using a CHW test based on re-weighted stratified logrank test statistics. If the re-estimated total number of events is equal to the initial planned total number of events, the CHW test will be reduced to the conventional stratified logrank test. Details of the CHW method will be described in the SAP.

The corresponding HR between treatment arms will be estimated using a stratified Cox regression model (Cox 1972), stratified by randomization strata. Progression free survival curves, medians, and PFS rates at various time points with 95% CI for each treatment arm will be estimated using the Kaplan-Meier method (Kaplan and Meier 1958).

PFS censoring scheme and sensitivity analyses will be described in the SAP.

9.4.3.2. Key Secondary Analyses

9.4.3.2.1. Treatment Failure Free Survival

Treatment Failure Free Survival (TFFS) per BICR is defined as the time from randomization to the first occurrence of:

- documented radiographic disease progression per RECIST 1.1 as assessed by BICR; or
- unacceptable toxicity leading to treatment discontinuation as assessed by the investigator. To qualify as an event, the toxicity must be from an intolerable AE (defined as any study drug-related AE that meets protocol guidance for treatment discontinuation, with the exception of alopecia); or
- death (due to any cause).

An independent review committee will review blinded data to determine whether an AE leading to treatment discontinuation meets protocol guidance and thus should be considered as a TFFS event. Independent review will occur retrospectively and will not impact patient care decisions or study conduct.

Since TFFS events include PFS events with additional events of treatment failure due to toxicity, TFFS is sufficiently powered as result of sample size determination based on PFS events. TFFS will be analyzed at the time of the final analysis which is triggered by the PFS events.

Conditional on achieving a statistical significance for the primary endpoint of PFS, TFFS will be tested in a manner that will preserve the 1-sided overall type I error rate at 2.5%:

- If the study remains at the initial planned total number of PFS events and sample size, the TFFS will be compared between treatment arms using a stratified logrank test, stratified by the 2 randomization strata based on IWRS data: RET mutation (M918T vs. other) and intended control treatment (cabozantinib vs. vandetanib).
- If the total number of PFS events required for the final analysis increases after sample size re-estimation, the TFFS will be compared between treatment arms using the CHW test in a similar manner of the primary efficacy analysis. Details will be described in the SAP.

The corresponding HR between treatment arms will be estimated using a stratified Cox regression model (Cox 1972), stratified by randomization strata. Treatment failure free survival curves, medians, and TFFS rates at various time points with 95% CI for each treatment arm will be estimated using the Kaplan-Meier method (Kaplan and Meier 1958).

TFFS censoring scheme and sensitivity analyses will be described in the SAP.

9.4.3.2.2. Comparative Tolerability

Comparative tolerability, as assessed by the FACT-GP5, is also a key secondary endpoint and will be tested conditionally on achieving a statistical significance for PFS and TFFS by BICR. Comparative tolerability will be defined as a comparison of the proportion of time on treatment with a high symptom burden as assessed by FACT-GP5 between Arm A and Arm B. A detailed analytical approach will be provided in the SAP.

Comparative tolerability will be assessed in the Tolerability Evaluable Population, i.e., patients enrolled by the time of the interim analysis (approximately 250 patients projected to be enrolled) regardless of the sample size re-estimation result. Since the sample size is fixed for the comparative tolerability endpoint, no adjustment of test statistic will be applied, and the type I error will not be inflated by a potential sample size increase.

9.4.3.2.3. Overall Survival

The study is not powered for OS but will continue to approximately 125 OS events or until a maximum of 6 years from the first patient visit, whichever comes first. If the true OS HR is 0.7, 125 OS events will provide approximately 98% probability that the observed OS HR would be less than 1.0, indicating no OS detriment associated with the selpercatinib treatment. A HR of 0.7 translates into a 42.9% relative and 30 months absolute increase in median OS (if assuming a median OS of 70 months for cabozantinib/vandetanib and 100 months for selpercatinib).

Overall survival (OS) is defined as the time from randomization until death from any cause. If the patient is alive or lost to follow-up at the time of data analysis, OS data will be censored on the last date the patient is known to be alive. Overall survival will be compared between treatment arms using a stratified log-rank test, stratified by the randomization strata for *RET* mutation (M918T vs. other) and intended treatment (cabozantinib vs. vandetanib). The

corresponding HR between treatment arms will be estimated using a stratified Cox regression model (Cox 1972), stratified by the randomization strata. Overall survival curves, the median and survival rates at various time points with 95% CI, for each treatment arm will be estimated using the Kaplan-Meier method (Kaplan and Meier 1958). Sensitivity analyses for OS will be described in the SAP.

9.4.3.3. Other Secondary Analyses

Overall response rate will be assessed for Arm A versus Arm B using a Cochran-Mantel-Haenszel test stratified by the randomization strata.

- ORR per RECIST 1.1 as assessed by BICR
- ORR per RECIST 1.1 per investigator assessment

The following secondary outcomes will be assessed for Arm A vs. Arm B using a logrank test stratified by the randomization strata. The corresponding HR between treatment arms will be estimated using a stratified Cox regression model (Cox 1972), stratified by the randomization strata. Point estimates with 95% CI, for each treatment arm will be estimated using the Kaplan-Meier method (Kaplan and Meier 1958).:

- TFFS as assessed by investigator
- PFS as assessed by investigator
- DoR as assessed by investigator
- DoR as assessed by BICR
- PFS2 as assessed by investigator

Progression-free survival per investigator assessment is defined in the same manner as BICR PFS.

TFFS per investigator assessment is defined as the time from randomization to the first occurrence of documented radiographic disease progression per RECIST 1.1 as assessed by the investigator or unacceptable toxicity leading to treatment discontinuation as assessed by the investigator (regardless of a study drug-related AE meets protocol guidance for treatment discontinuation or not); or death (due to any cause).

Progression-free survival 2 (PFS2) is defined as the time from randomization to disease progression (radiographic or symptomatic progression as determined by the investigator) on the next line of treatment or death from any cause in the absence of observed disease progression. If the patient is alive at the cutoff for analysis, and disease progression has not been observed, PFS2 data will be censored on the latest date of last progression-free assessment or start of the next line of treatment.

Duration of response (DOR) is defined as the time from the date that measurement criteria for complete response (CR) or partial response (PR) (whichever is first recorded) are first met by the BICR or investigator assessment, as applicable, until the first date that disease is recurrent or documented disease progression is observed, per RECIST 1.1 criteria, or the date of death from any cause in the absence of documented disease progression or recurrence.

Overall response rate (ORR) is defined as the number of patients who achieve a best overall response (BOR) of CR or PR divided by the total number of patients randomized to each treatment arm. The ORR, with 95% CI, will be summarized for each treatment arm.

Best overall response is determined from a sequence of responses assessed. Two objective status determinations of CR before progression are required for a best response of CR. Two determinations of PR before progression, but not qualifying for a CR, are required for a best response of PR. The second objective response is required to be ≥28 days after the initial response.

9.4.3.4. RET-Testing Concordance Analysis

The concordance between *RET* testing results based on local laboratory tests and centrally assessed results will be evaluated. Details regarding analyses involving centrally assessed *RET*-testing results will be described in a separate Diagnostics SAP.

9.4.3.5. Tertiary/Exploratory Analyses

The following endpoints with be assessed as tertiary/exploratory analyses, with detailed methods provided in the SAP:

Time to initiation of new anticancer therapy, defined as the time from randomization to documentation in the CRF of a new local (e.g., surgery, radiation) or systemic anticancer treatment administered to the patient.

PFS after crossover, defined as the time from start of selpercatinib treatment until the occurrence of disease progression or death from any cause for crossover population.

Calcitonin and CEA response rate, defined as percentage of patients who had a decline from baseline in the calcitonin or CEA level of at least 50% maintained for at least 4 weeks.

9.4.4. Safety Analyses

Detailed tabulations of safety data (AEs and clinical laboratory tests) will be provided for all subjects receiving the study drug. The number and percent of subjects with TEAEs will be summarized. Summary of other safety parameters by treatment group will be provided where appropriate.

Safety data after crossover will be summarized for crossover population. TEAEs and clinical laboratory abnormalities will be defined according to the crossover baseline with details provided in the SAP.

9.4.5. Pharmacokinetic/Pharmacodynamic Analyses

Selpercatinib plasma concentrations will be summarized by descriptive statistics and graphics. Additionally, the data will be evaluated through population PK methodology.

The relationship between selpercatinib plasma exposure and pharmacodynamic markers, such as tumor size, efficacy, as well as selected safety outcomes, will be explored.

9.4.6. Biomarker Analysis

Biomarker results will be summarized and may be analyzed for correlations with clinical outcomes.

9.4.7. Other Analyses

9.4.7.1. Health Economics

9.4.7.1.1. Patient Reporting Outcomes (PROs)

For each instrument, percentage compliance will be calculated as the number of completed assessments divided by the number of expected assessments. Data will be separately summarized using descriptive statistics.

Further details will be provided in the SAP for each PRO instrument, respectively.

9.4.7.1.2. Healthcare Resource Utilization

Frequency counts of hospitalizations, duration of stay, emergency room visits, GCSF use, transfusions and analgesic use will be reported descriptively for each treatment arm by cycle.

9.4.7.2. Subgroup Analyses

To determine whether the treatment effect is consistent across various subgroups, the between-group treatment effect for OS, PFS, TFFS and ORR (with a nominal 95% CI) will be estimated and plotted within each category of the following subgroups (defined based on eCRF data):

- Age category (≤65 vs. >65 years)
- ECOG Performance Scale (0-1 vs. 2)
- Sex (female vs. male)
- Race (Asian vs. non-Asian)
- Tissue vs. blood *RET* mutation detection
- *RET* mutation: M918T vs. other
- Investigator's choice of treatment with cabozantinib vs. vandetanib

If a level of a factor includes fewer than 5% of the ITT population, analysis within that level will be omitted. Additional subgroup analyses may be performed as deemed appropriate.

9.5. Interim Analyses

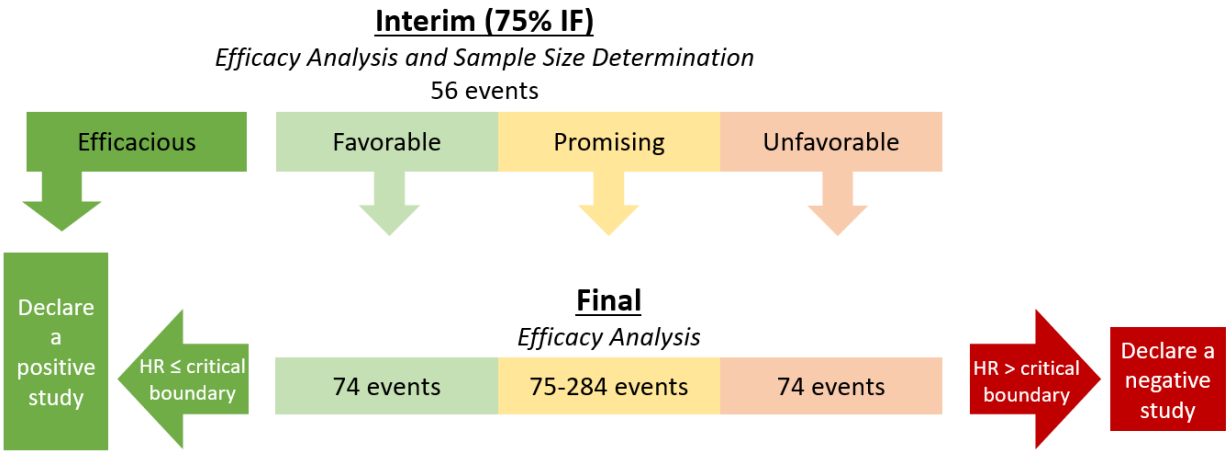
An interim analysis will be triggered after approximately 56 PFS events by BICR have occurred (at 75% information fraction). Based on the observed HR of PFS by BICR and pre-specified criteria, the study results at interim analysis will be categorized into 4 determination zones: efficacious, favorable, promising, and unfavorable.

- If the study results fall into the **efficacious** zone, a positive study will be declared due to overwhelming efficacy, enrollment will be stopped, and regulatory interactions will be initiated.

- If the study results fall into the **favorable** zone, the study will continue to the final analysis with the initially planned total number of events at 74 (i.e., no re-estimation will be conducted).
- If the study falls into the **promising** zone, the total number of events will be increased. The events re-estimation will be based on the observed PFS HR according to the method provided in Cui et al. (1999). The total number of patients will be increased and determined accordingly so that the required number of events could be achieved in a desired timeframe.
- If the study results fall into the **unfavorable** zone, enrollment will be halted, and the study will continue to the final analysis.

The criteria for each zone will be prespecified in the Adaptive Design Charter.

The figure below provides an overview of the proposed adaptive design. At the pre-specified interim efficacy analysis, the sample size/total number of events for the final analysis will be determined. If the study is not declared positive, final analysis will be conducted according to a determination zone (favorable, promising, or unfavorable), based on where the interim results fall. At final analysis, the study will be declared positive if the critical boundary is met. To preserve the type I error, the Rho family alpha spending function (Kim and DeMets 1987) will be used to account of multiple analyses, and a weighted test statistic proposed in the CHW method will be used as the primary test at final analysis. All significance levels and weights in CHW method will be based on the actual number of events observed at the time of analyses.



Abbreviations: IF=Information Fraction; HR=Hazards Ratio

An independent Data Monitoring Committee (IDMC) will be established to conduct interim efficacy and safety analyses and will follow an approved IDMC charter. The IDMC may initiate a consultation with an appropriate expert (such as cardiac) if additional expertise is needed regarding evaluation of any safety signals. The IDMC will communicate back to a Lilly Senior Management Designee (SMD) about their assessment.

An early safety analysis will be performed after approximately 50 subjects have been randomized and had the opportunity to be treated for 2 cycles. This analysis will focus on deaths, treatment discontinuations, SAEs, and Grade 3/4 AEs. The IDMC will meet and review data

approximately every 6 months thereafter. Detailed information on the role of the IDMC and frequency of meetings will be provided in the IDMC charter separate from this protocol.

For interim efficacy analysis and the sample size re-estimation, the IDMC will be provided with pre-specified decision rules as described in the Adaptive Design Charter. The SAC will be responsible for preparing and reporting interim efficacy analysis results to the IDMC. This practice will ensure that Lilly personnel involved in the day-to-day management and conduct of the trial do not have access to unblinded comparative results, even inadvertently. The IDMC will review unblinded results and make a recommendation on declaring the study positive for overwhelming efficacy or continuing the study with a certain total number of events according to the plan. IDMC recommendations will exclude any details of the interim efficacy analysis results.

Following the determination of the required number of events for the final analysis by the IDMC, Lilly study team will confirm the total number of patients in order to ensure achievement of the required number of events for the final analysis. This determination will be made in a blinded manner using the pooled PFS data.

10. Supporting Documentation and Operational Considerations

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

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH GCP Guidelines
  - Applicable laws and regulations

- The protocol, protocol amendments, ICF, Investigator Brochure, 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
  - Reporting to the sponsor or designee significant issues related to participant safety, participant rights, or data integrity

After reading the protocol, each principal investigator will sign the protocol signature page and send a copy of the signed page to a Lilly representative.

The CSR coordinating investigator will sign the final CSR for this study, indicating agreement that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

10.1.2. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the participant 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 (HIPAA) 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.

Participants who are rescreened are required to sign a new ICF.

10.1.3. Data Protection

- Participants will be assigned a unique identifier by the sponsor to protect the participant's personal data. Any participant information, such as records, datasets or tissue samples that are transferred to the sponsor will contain the identifier only. Participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that the participant's personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent. This is done by the site personnel through the informed consent process.
- The participant must be informed through the informed consent by the site personnel that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The sponsor has processes in place to ensure information security, data integrity, and data protection. These processes address management of data transfer and prevention and management of unauthorized access, disclosure, dissemination, alteration, or loss of information or personal data. These processes include appropriate contingency plan(s) for appropriate and timely response in the event of a data security breach.
- The transfer of personal data is subject to appropriate safeguards through contractual agreements and processes. The sponsor's processes are compliant with local privacy laws and relevant legislations including the General Data Protection Regulation (GDPR).

10.1.4. Committees Structure

The primary endpoint TFFS will be assessed by BICR. The BICR will be composed of independent radiologists to perform response assessments and determination of disease progression per RECIST 1.1 and if needed, independent clinicians to review the case report forms (CRF) and determine whether discontinuation for unacceptable toxicity meets the criteria for a TFFS event as defined above

10.1.5. Dissemination of Clinical Study Data

Dissemination of study data will be performed according to all applicable Lilly and international policies.

Reports

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

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

10.1.6. Data Quality Assurance

To ensure accurate, complete, and reliable data, the sponsor or its representatives will do the following:

- provide instructional material to the study sites, as appropriate
- provide sponsor start-up training to instruct the investigators and study coordinators. This training will give instruction on the protocol, the completion of the CRFs, 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, and/or fax
- review and verify data reported to detect potential errors

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.

The investigator will keep records of all original source data. This might include laboratory tests, medical records, and clinical notes. If requested, the investigator will provide the sponsor, applicable regulatory agencies, and applicable ERBs with direct access to original source documents.

Data Capture System

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

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

Additionally, electronic Clinical Outcome Assessment (eCOA) data questionnaires and scales will be directly recorded by the patient, into an instrument (e.g., an electronic device). The eCOA data will serve as the source documentation and the investigator does not maintain a separate, written or electronic record of these data.

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

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

Data from complaint forms submitted to Lilly 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 eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

10.1.8. Study and Site Closure

10.1.8.1. Discontinuation of the Study

The study will be discontinued if Lilly judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

10.1.8.2. Discontinuation of Study Sites

Study site participation may be discontinued if Lilly, the investigator, or the ERB of the study site judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

10.1.9. Provisions for Changes in Study Conduct During Emergencies

There may be times due to exceptional circumstances where it may not be feasible for patients to come to investigator sites for study-required visits. To mitigate the risk of patients missing visits, to allow patients to safely continue to receive care, and maintain the data integrity of the study, the following may be allowed on a case-by-case basis following approval from the sponsor and if permitted by local regulations.

- Remote/virtual visits and/or extended visit windows may be used. Medically qualified site personnel may collect study required information (e.g., AEs, concomitant medications, ECOG status, and study treatment compliance) via videoconference (preferred) or phone. Visit or cycle windows as defined in the schedule of activities may be extended to facilitate the ability to perform study-specific assessments at the site, which is preferred to remote/virtual visits. Every effort should be made to return to in-clinic visits as soon as reasonably possible and safe for the patient and investigator/site staff.
- Labs, ECGs and/or tumor imaging may be obtained at a local (non-study) site. Laboratory results (including reference ranges), ECGs and/or scans obtained at a local lab must be filed and reviewed by the study investigator or qualified designee in a timely manner.
- For patients that meet the protocol criteria to continue or restart dosing, local processes may be leveraged to deliver drug directly to patients.
- A remote informed consent process may be implemented.

Site personnel are responsible for documenting in the source records all changes in study conduct, relevant communications (patient and sponsor), and dispensing/shipment records of IP and indicating the actions taken as a result of exceptional circumstances mitigation. If mitigations are approved by the sponsor, additional instructions on the process and documentation will be provided to the site. Additional mitigations may be approved by the sponsor and will be tracked as protocol deviations as required.

10.2. Appendix 2: Clinical Laboratory Tests

The tests detailed below will be performed by the indicated laboratory.

- Local laboratory results are required only in the event that the central laboratory results are not available in time for inclusion/exclusion determination, study intervention administration, and/or response evaluation or for assessments that are performed remotely/virtually. If a local sample is required, it is important that the sample for central analysis is obtained at the same time (e.g., hepatic safety labs). Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, this should be reported into the CRF as an AE. If there is an abnormal laboratory value or abnormal value for any other diagnostic or screening test (e.g., blood pressure increased, neutrophils decreased, etc.) and it is known to be related to a diagnosis (e.g., hypertension, neutropenia, etc.) this should be reported into the CRF as an AE. Do not enter the test abnormality, enter the disease diagnosis or categorical term.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations, and clinically significant findings should be reported in the CRF as an AE.
- Enrollment and treatment decisions may be based upon local laboratory results. Discrepancies between local and central laboratory results will not be considered a protocol deviation.

Hematology – local laboratory

- Leukocytes (WBC)
- Neutrophils[a]
- Lymphocytes
- Monocytes
- Eosinophils
- Basophils
- Erythrocytes (RBC)
- Hemoglobin (HGB)
- Hematocrit (HCT)
- Platelets (PLT)

Coagulation – local laboratory

- Activated partial thromboplastin time (aPTT) or partial thromboplastin time (PTT)
- International normalized ratio (INR) or prothrombin time (PT)

Chemistry –central laboratory[b,c]

Serum concentrations of:

- Alanine aminotransferase (ALT)
- Albumin
- Alkaline phosphatase
- Aspartate aminotransferase (AST)
- Bicarbonate
- Bilirubin, total
- BUN or blood urea
- Calcium
- Chloride
- Creatinine
- Glucose, random
- Magnesium
- Phosphorus
- Potassium
- Sodium
- Total protein

Hepatic monitoring –central laboratory[b,c]

- Alanine aminotransferase (ALT)
- Aspartate aminotransferase (AST)
- Alkaline phosphatase
- Bilirubin, direct
- Bilirubin, total

Thyroid panel – local laboratory • Triiodothyronine (T3) (free or total, per local standard of care) • Thyroxine (T4) (free or total, per local standard of care) • Thyroid stimulating hormone (TSH)
Calcitonin, CEA – central laboratory
Cortisol, ACTH– local laboratory
Pregnancy test (for female patients of childbearing potential) – local laboratory • Urine or serum, per institutional standard • Urine pregnancy test, if used, must have a minimum sensitivity of 25 IU/L or equivalent units of β-hCG. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required
Urine protein – local laboratory [d]

Abbreviations: BUN = blood urea nitrogen; DNA = deoxyribonucleic acid; RBC = red blood cells; RNA = ribonucleic acid; T4 = thyroxine; TSH = thyroid-stimulating hormone; WBC = white blood cells.

Note: Study eligibility and decisions about treatment will be based on local laboratory results.

[a] Neutrophils reported by automated differential hematology instruments include both segmented and band forms. When a manual differential is needed to report the neutrophils, the segmented and band forms should be added together and recorded on the CRF, unless the CRF specifically provides an entry field for bands.

[b] Treatment and enrollment decisions should be based on local laboratory results. Investigators may use central laboratory results to guide treatment and enrollment decisions if local laboratories are not available. Local laboratory results are not required to be recorded on a CRF if a sample is sent to the central laboratory at the same time.

[c] Central laboratory may be used for Lilly investigational analysis.

[d] If urine dipstick shows a positive result then sample should be sent for urinalysis.

10.3. Appendix 3: Contraceptive Guidance and Collection of Pregnancy Information

Definitions:

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal 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 WOCBP

1. Premenarchal
2. Premenopausal female with one of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy
   - For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

   Note: Documentation can come from the site personnel: review of the participant's medical records, medical examination, or medical history interview.
3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
   - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
   - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance:

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods[b] That Have Low User Dependency
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)[c]
• Bilateral tubal occlusion
• Vasectomized partner • *(Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.)*
Highly Effective Methods[b] That Are User Dependent
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c] o oral o intravaginal o transdermal o injectable
• Progestogen-only hormone contraception associated with inhibition of ovulation[c] o oral o injectable
• Sexual abstinence *(Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)*

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

[b] Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.

[c] If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.

Note: Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception for this study. Male condom and female condom should not be used together (due to risk of failure with friction).

Collection of Pregnancy Information

Male participants with partners who become pregnant

- The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive study intervention.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female Participants who become pregnant

- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a participant's pregnancy.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of 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 will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any post-study pregnancy related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.3.2. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention or be withdrawn from the study.

10.4. Appendix 4: Liver Safety: Suggested Actions and Follow-up Assessments

Selected tests may be obtained in the event of a treatment-emergent hepatic abnormality and may be required in follow-up with patients in consultation with the Lilly medical team. In general, the labs below should be sent at first occurrence of Grade ≥3 elevated hepatic lab increases (ALT, AST, or direct bilirubin). For subsequent occurrences, these labs may be repeated at the discretion of the investigator.

Hepatic Safety Tests	
Hepatic Hematology[a]	**Haptoglobin[a]**
Hemoglobin (HGB)	
Hematocrit (HCT)	**Hepatic Coagulation[a]**
Erythrocytes (RBC)	Prothrombin time (PT)
Leukocytes (WBC)	Prothrombin time, INR
Neutrophils[b]	
Lymphocytes	**Hepatic Serologies[a,c]**
Monocytes	Hepatitis A antibody, total
Eosinophils	Hepatitis A antibody, IgM
Basophils	Hepatitis B surface antigen
Platelets (PLT)	Hepatitis B virus DNA[c]
	Hepatitis B surface antibody
Hepatic Chemistry[a]	Hepatitis B Core antibody
Total bilirubin	Hepatitis C antibody
Direct bilirubin	Hepatitis C virus RNA PCR[c]
Alkaline phosphatase	Hepatitis E antibody, IgG
Alanine aminotransferase (ALT)	Hepatitis E antibody, IgM
Aspartate aminotransferase (AST)	Hepatitis E virus RNA PCR[c]
Gamma-glutamyl transferase (GGT)	
Creatine phosphokinase (CPK)	**Recommended Autoimmune Serology**
	Anti-nuclear antibody[a]
	Anti-smooth muscle antibody[a]
	Anti-actin antibody[a]

Abbreviations: CRF = case report form; IgG = immunoglobulin G; IgM = immunoglobulin M; INR = international normalized ratio; RBC = red blood cells; WBC = white blood cells.

[a] Assayed by central laboratory.

[b] Neutrophils reported by automated differential hematology instruments include both segmented and band forms. Whenever a manual differential is needed to report the neutrophils, the segmented and band forms should be added together and recorded on the CRF, unless the CRF specifically provides an entry field for bands.

[c] Reflex/confirmation dependent on regulatory requirements and/or testing availability.

10.5. Appendix 5: Country-specific Requirements

10.5.1. Discontinuation of Inadvertently Enrolled Patients in the UK and Germany

If the sponsor or investigator identifies a participant who did not meet enrollment criteria and was inadvertently enrolled, then the participant should be discontinued from study treatment and safety follow up should be performed as outlined in Section 1.3 (Schedule of Activities), Section 8.3 (Adverse Events and Serious Adverse Events), and Section 8.2 (Safety Assessments) of the protocol.

10.6. Appendix 6: *RET* activating mutations in MTC

Exon	*RET* mutation
5	V292M, G321R
8	A510V, E511K, C515S, C531R, G533C
10	V591I, R600Q, K603E/Q, Y606C, C609F/G/R/S/W/Y, C611F/G/R/S/W/Y, C618F/G/R/S/W/Y, C620F/G/R/S/W/Y
11	C630R/Y, D631Y, E632K, C634F/G/R/S/W/Y, S649L, K666E/M
13	E768D, R770Q, N777S, V778I, Q781R, L790F
14	V804L, V804M, Y806C, E819K, R833C, R844Q, R866W, M848T
15	L881V, A883F/S/T/V, R886W, S891A, S904F
16	S904C/F, G911D, R912P, M918T, E921K, S922P, T930M
Complex	D631del, E632-L633del, D898-E901del, E632-A639> HR
Other	Because the list of published activating *RET* mutations is constantly being updated, other mutations (e.g. other complex mutations, overlapping deletions, substitutions with different amino acids at the same site) may be eligible if a compelling rationale is provided by the Investigator and approved by the sponsor.
No other known validated MTC driver alteration(s). These include *RAS or BRAF* gene mutations and *NTRK* gene fusions.	
Mutation identified in a tumor, germline DNA or blood sample according to laboratory with CLIA, ISO/IEC, CAP, or similar certification, as long as a written Molecular Pathology Report is available and clearly asserts the presence of the referenced *RET* alteration (Dvorakova et al. 2008, Agrawal et al. 2013, Krampitz et al. 2014, Ji et al. 2015, Wells et al. 2015, Heilmann et al. 2016, Romei et al. 2016, Kato et al. 2017).	

Abbreviations: CAP-College of American Pathologists; CLIA-Clinical Laboratory Improvement Amendments; ISO/IEC-International Organization for Standardization/Independent Ethics Committee; MTC-medullary thyroid cancer.

10.7. Appendix 7: Restricted and Prohibited Concomitant Medications

The table(s) below describes the drug class and associated medications that will be restricted or prohibited during the study treatment period.

This is not an all-inclusive list; in general, all strong and moderate CYP3A4 inhibitors, strong and moderate inducers of CYP3A4, sensitive CYP2C8 substrates, and protein pump inhibitors (PPI's) are restricted during the study treatment period. Agents known to cause QTc prolongation are prohibited in patients receiving selpercatinib or vandetanib during the study treatment period.

Note: Non-systemic (e.g., topical creams, eye drops, mouthwashes, etc.) applications of the following are permissible.

Inhibitors of CYP3A4	
Strong Inhibitors[a]	**Moderate Inhibitors**[b]
boceprevir	Amprenavir
clarithromycin	Atazanavir
conivaptan	Ciprofloxacin
grapefruit juice[c]	Darunavir
Indinavir	Diltiazem
Itraconazole	Erythromycin
Ketoconazole	Fluconazole
Lopinavir	Fosamprenavir
Mibefradil	Imatinib
Nefazodone	Verapamil
Nelfinavir	
Posaconazole	
Ritonavir	
Saquinavir	
Telaprevir	
Telithromycin	
Voriconazole	

Abbreviations: AUC = area under the concentration versus time curve; CYP3A4 = cytochrome P450 3A4.

[a] Increases the AUC of sensitive index substrates of a given metabolic pathway by ≥5-fold.

[b] Increases the AUC of sensitive index substrates of a given metabolic pathway by 2- to 5-fold.

[c] When excessive amounts are consumed.

Inducers of CYP3A4	
Strong Inducers[a]	**Moderate Inducers**[b]
Avasimibe	Bosentan
Carbamazepine	Efavirenz
Enzalutamide	Etravirine
Phenytoin	Modafinil
Rifampin	Nafcillin
St John's wort	

Abbreviations: AUC-area under the concentration versus time curve; CYP3A4-cytochrome P450 3A4.

[a] Decreases the AUC of the sensitive index substrates of a given metabolic pathway by ≥ 80%.

[b] Decreases the AUC of the sensitive index substrates of a given metabolic pathway by 50–80%.

Sensitive CYP2C8 substrates
Repaglinide
Dasabuvir
Selexipag

Examples of Proton Pump Inhibitors (PPIs)	
omeprazole	pantoprazole
esomeprazole	rabeprazole
lansoprazole	dexlansoprazole

Note: The above lists are not exhaustive. See also: http://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm.

Examples of Agents Known to Cause QTc Prolongation	
Amiodarone	ibogaine
Anagrelide	Ibutilide
Azithromycin	levofloxacin
Chloroquine	levomepromazine (methotrimeprazine)
Chlorpromazine	levosulpiride
Cilostazol	Methadone
Ciprofloxacin	moxifloxacin
Citalopram	Ondansetron
Clarithromycin	papaverine HCl (intracoronary)
Cocaine	Pentamidine
Disopyramide	Pimozide
Dofetilide	procainamide
domperidone	Propofol
Donepezil	Quinidine
Dronedarone	roxithromycin
Droperidol	Sevoflurane
Erythromycin	Sotalol
Escitalopram	sulpiride
Flecainide	sultopride
Fluconazole	terlipressin
halofantrine	terodiline
Haloperidol	Thioridazine
hydroquinidine, dihydroquinidine	

Note: The above list is not exhaustive. Please refer to https://www.crediblemeds.org/for a current list of agents known to cause QTc prolongation as well as agents with a possible or conditional risk.

Examples of H2 blocking agents	
Famotidine	cimetidine
Ranitidine	nizatidine

Note: The above lists are not exhaustive. See also: http://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm

10.8. Appendix 8: Country-Specific Requirements

The country-specific addenda presented in this appendix must be performed in each of the respective countries, in addition to all procedures required by current version of Protocol J2G-MC-JZJB (JZJB) where applicable. The consolidation of these country-specific addenda into this appendix is to facilitate transition of this trial to the CTIS system under the new clinical trial regulation in Europe.

10.8.1. Addendum 3.1 (Country-Specific Content for Germany)

This addendum addresses the additional requirements for Study JZJB sites in Germany.

The following table describes the changes being made to Protocol JZJB for participants in Germany.

Main Protocol Section # and Name	Description of Change
5.1. Inclusion Criteria	Modified criterion 1 to remove text related to allowing participants as young as 12 years of age.

Protocol Revisions

For JZJB Protocol Addendum, additions have been identified by use of underscore and deletions have been identified by ~~strikethrough~~.

Section 5.1. Inclusion Criteria

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

Age

1. Are of an acceptable age to provide informed consent according to local regulations and are at least 18 years of age ~~(patients as young as 12 years of age will be allowed if permitted by local regulatory authorities and institutional review boards)~~.

10.8.2. Addendum 8 (Country-Specific Content for the Netherlands)

This addendum addresses feedback from the METC of the Netherlands Cancer Institute (Central Ethics Review Board).

The following table describes the changes being made to Protocol JZJB for participants in the Netherlands.

Main Protocol Section # and Name	Description of Change
5.1. Inclusion Criteria	Modified criterion 1 to allow participants at least 16 years of age.

Protocol Additions

Section 5.1. Inclusion Criteria

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

Age

1. Are of an acceptable age to provide informed consent according to local regulations and are at least 16 years of age.

10.8.3. Addendum 10 (Country-Specific Content for the Czech Republic)

This addendum addresses feedback from The Czech Competent Authority (Státní ústav pro kontrolu léčiv (SUKL).

The following table describes the changes being made to Protocol JZJB for participants in the Czech Republic.

Main Protocol Section # and Name	Description of Change
1.3.2. Screening, On-Study, and Post-Study Treatment Follow-Up Schedule of Activities for Patients on Arm A and Arm B	After screening period pregnancy test 24 hours prior to first dose, a monthly pregnancy test must be performed on women of child-bearing potential during study drug treatment
1.3.4. Optional Crossover Treatment (for patients crossing over from Arm B to Arm A)	After screening period pregnancy test 24 hours prior to first dose, a monthly pregnancy test must be performed on women of child-bearing potential during study drug treatment

Protocol Additions

Section 1.3.2. Screening, On-Study, and Post-Study Treatment Follow-Up Schedule of Activities for Patients on Arm A and Arm B

Screening, On-Study, and Post-Study Treatment Follow-Up Schedule of Activities for Patients on Arm A and Arm B															
	Screening		**On-Treatment Cycle = 28 days**								**Safety assessments prior to crossover (only for patients on Arm B)**		**Post-Study Treatment**		
	(Day Relative to C1D1)		**Cycle 1**				**Cycle 2-n**				**V201[a]**		**Short-term Follow-up[a]**	**Long term Follow-up[b]**	**Instructions**
			(±3 days)				(±3 days)				Day 1-30 (±7 days)	1-x days	(30 ± 7 days)	(90 ± 14 days)	
	≤28	**≤7**	**D1**	**D8**	**D15**	**D22**	**D1**	**D8**	**D15**	**D22**	**N/A**	**N/A**	**V801**	**V802-8XX**	
Procedure															
Pregnancy Test		X	X	See Instructions							See Instructions		X		Applies only to women of childbearing potential. • Note: during study treatment, perform at screening, C1D1 (within 24 hours prior to first dose of study drug), and monthly (+/-7 days) thereafter as required per local regulations and/or institutional guidelines. • See Appendix 2

Section 1.3.4. Optional Crossover Treatment (for patients crossing over from Arm B to Arm A)

Optional Crossover Treatment (for patients crossing over from Arm B to Arm A)												
	Crossover Screening	**On-Treatment Cycle = 28 days**								**Post-Study Treatment**		**Instructions**
	Visit 300 (Day relative to start of treatment)	**Visit 301 Cycle 1**				**Visit 302-n Cycle 2-n**				**Short-term Follow-up[a]**	**Long term Follow-up[b]**	
		(±3 days)				(±3 days)				(30 ± 7 days)	(90 ± 14days)	
	≤42	**D1**	**D8**	**D15**	**D22**	**D1**	**D8**	**D15**	**D 22**	**V801**	**V802-8XX**	
Procedure												
Pregnancy Test	X	X	See Instructions							X		• Applies only to women of childbearing potential. • Note: during study treatment, perform C1D1 (within 24 hours prior to dose) and monthly (+/-7 days) thereafter as required per local regulations and/or institutional guidelines. • See Appendix 2.

10.8.4. Addendum 11 (Country-Specific Content for Belgium)

This addendum addresses protocol items to comply with local laws and regulatory requirements in Belgium.

The following table describes the changes being made to Protocol JZJB for participants in Belgium.

Main Protocol Section # and Name	Description of Change
5.1. Inclusion Criteria	Modified criterion 10 to add duration of 4 months regarding the use of a highly effective contraceptive method following the last dose of study drug. Removed text related to condom use. Modified criterion 11 to add text regarding use of highly effective contraceptive method for at least 4 months after the last dose of study drug.
5.2. Exclusion Criteria	Modified criterion 26 to add having known hypersensitivity to any of the excipients of "selpercatinib".
6.5. Concomitant Therapy	Added sentence indicating that caution should be used when co-administration of P-gp, MATE1, or BCRP substrates cannot be avoided in patients receiving selpercatinib.
6.5.1. CYP3A4 Inducers or Inhibitors	Added text regarding the co-administration of selpercatinib with sensitive CYP3A4 substrates.
1.3.2. Screening, On-Study, and Post-Study Treatment Follow-Up Schedule of Activities for Patients on Arm A and Arm B	Modified text in Instructions column for pregnancy test timing to meet local regulations.

Protocol Additions

The revised text in the following sections show the changes applicable to patients in Belgium. All additions have been identified by the use of underscore; and deletions have been identified by ~~strikethrough~~.

Sections 5.1. and 5.2. Inclusion and Exclusion Criteria

10. Men with partners of childbearing potential or women of childbearing potential must agree to use a highly effective contraceptive method (for example, intrauterine device [IUD], birth control pill, or barrier method) during treatment with study drug and for 4 months following the last dose of study drug (for men and women). ~~If a condom is used as a barrier contraceptive, a spermicidal agent should be added as double-barrier protection.~~ See Appendix 3.

Note: Unless not allowed by local regulations, women 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 unless they agree to use contraceptive method known to be highly effective.

Periodic abstinence (e.g., calendar, ovulation, symptothermal, postovulation methods), declaration of abstinence just for the duration of a trial, and withdrawal are not acceptable methods of contraception.

11. Women of childbearing potential must

- have a negative pregnancy test (serum or urine, consistent with local regulations) documented within 24 hours prior to treatment with study drug.
- not be breast-feeding during treatment and for at least 4 months after the last dose of study drug.
- agree to use a highly effective contraceptive method for at least 4 months after the last dose of study drug.

26. Have a known hypersensitivity to any of the excipients of either cabozantinib, ~~or~~ vandetanib, or selpercatinib.

Section 6.5. Concomitant Therapy

Patients receiving selpercatinib should avoid concomitant use of CYP2C8-sensitive substrates. If co-administration of a CYP2C8-sensitive substrate cannot be avoided, monitor patients for increased adverse reactions of these drugs.

Caution should be used when co-administration of a P-gp substrate (e.g., fexofenadine, loperamide, digoxin), MATE1 substrate (e.g., metformin) or BCRP substrate (e.g., sulfasalazine) cannot be avoided in patients receiving selpercatinib. Consider increased monitoring as appropriate.

Section 6.5.1. CYP3A4 Inducers or Inhibitors

For patients receiving selpercatinib: The concomitant use of the strong CYP3A4 inhibitors or inducers should be avoided. See Appendix 7.

If, during the study, patients require initiation of treatment with strong inhibitors or inducers of CYP3A4 for clinical reasons, investigators should consider increased monitoring for the development of new AEs.

Co-administration of selpercatinib with sensitive CYP3A4 substrates may increase their plasma concentrations, which may increase the incidence or severity of adverse reactions for sensitive substrates with narrow therapeutic windows.

Section 1.3.2. Screening, On-Study, and Post-Study Treatment Follow-Up Schedule of Activities for Patients on Arm A and Arm B

Screening, On-Study, and Post-Study Treatment Follow-Up Schedule of Activities for Patients on Arm A and Arm B															
	Screening		**On-Treatment Cycle = 28 days**								**Safety assessments prior to crossover (only for patients on Arm B)**		**Post-Study Treatment**		
	(Day Relative to C1D1)		**Cycle 1**				**Cycle 2-n**				**V201[a]**		**Short-term Follow-up[a]**	**Long term Follow-up[b]**	**Instructions**
			(±3 days)				(±3 days)				Day 1-30 (±7 days)	1-x days	(30 ± 7 days)	(90 ± 14 days)	
	≤28	**≤7**	**D1**	**D8**	**D15**	**D22**	**D1**	**D8**	**D15**	**D22**	**N/A**	**N/A**	**V801**	**V802-8XX**	
Procedure															
Pregnancy test		X	X	See Instructions			X	See Instructions			See Instructions		X		• Applies only to women of childbearing potential. • Note: during study treatment, perform at screening, C1D1(within 24 hours prior to first dose of study drug), and on day 1 of each 28 day treatment cycle ~~thereafter~~ as required per local regulations ~~and/or institutional guidelines~~. • See Appendix 2

10.8.5. Addendum 12.2 (Country-Specific Content for Czech Republic, Germany, Italy, Netherlands, Poland, Spain, Brazil, United States, United Kingdom, Australia, and Canada)

This addendum addresses protocol items to comply with local laws and regulatory requirements in the Czech Republic, Germany, Italy, Netherlands, Poland, Spain, Brazil, United States, United Kingdom, Australia, and Canada.

The following table describes the changes being made to Protocol JZJB.

Main Protocol Section # and Name	Description of Change
Addition of addendum	Details how a study participant's perspective on the secondary endpoint of comparative tolerability will be obtained and evaluated

1. Rationale for Addendum

This addendum is part of a comprehensive research plan related to the secondary endpoint of the trial evaluating comparative tolerability. This addendum details how a study participant's perspective on the secondary endpoint of comparative tolerability will be obtained and evaluated.

J2G-MC-JZJB (JZJB) includes a comparative tolerability endpoint as a key secondary outcome based on the comparison of high-side-effect bother of study treatment arms as assessed by the FACT-GP5. In addition to the quantitative data collection and analyses described in the protocol, complementary qualitative data via semi-structured participant interviews will be obtained at the sites in participating countries. To understand if the FACT-GP5 captures the participant experience and to explore factors related to the endpoint definition and responder threshold, the sponsor seeks to solicit direct feedback from participants about these concepts. An appendix titled "Participant Interview Guide" has been added as supporting documentation to this addendum describing the interview procedure.

2. Qualitative Interviewing Research Plan

2.1. Objectives

The overall objectives of these qualitative interviews are to understand

1) The concept of tolerability from the participant's perspective

   a. Experience of symptomatic (participant-felt) adverse events (AEs) since initiating study treatment in the clinical trial

      i. Description of symptomatic AEs

      ii. Onset or trajectory of symptomatic AEs

      iii. Bother or burden of these AEs, including most bothersome or least bothersome AE(s), and

      iv. Impact of AEs on their lives.

2) Interpretation or meaning of the concepts associated with the endpoint, and

a. Side-effect bother

b. Side-effect burden, and

c. Tolerability.

3) How participants interpret the FACT-GP5 item and response choices, including their perception of which response option constitutes "high-side-effect bother" and at what point they would speak to their doctor about changing the treatment or stopping/discontinuing the treatment ("impacts their ability or desire to adhere to the dose or intensity of therapy").

2.2. Methodology

2.2.1. Overview

An independent vendor (Modus Outcomes®) paid by the sponsor will interview a subset of participants who are enrolled in Study JZJB. Enrollment will continue until conceptual saturation has been reached (described below). These interviews will comprise 2 parts, (a) concept elicitation to collect information about the participant's experience of side effects and their interpretation or meaning of the concepts associated with the endpoint, and (b) cognitive debriefing of the FACT-GP5 item (a patient-reported outcome [PRO] question that assesses the overall burden of side effects) to assess participants' interpretation of the item and response choices. These interviews will be recorded, transcribed, and analyzed using inductive thematic coding. Modus Outcomes will follow the sponsor's data management and pharmacovigilance policies.

2.2.2. Study Steps

2.2.2.1. Site Initiation Meetings

Modus Outcomes will schedule a virtual meeting with site coordinators to describe the nature of the qualitative interviews and explain the screening process, the procedure to obtain informed consent, and the process by which to securely send contact information to Modus Outcomes. This meeting will be a 30-minute telephone call and provides a base knowledge for site coordinators and study personnel about the qualitative study.

Modus Outcomes will send a confirmation email to sites after the site initiation meeting has taken place to serve as a record of completion. This communication will also provide sites with Modus Outcomes' contact information should any screening or consent questions arise during the course of the study that need immediate attention.

2.2.2.2. Scheduling Participants

Once a participant consents to being contacted, the site will send Modus Outcomes a copy of this completed form using a secure cloud-based upload (Citrix ShareFile). The original consent form will be stored at the site. A Modus Outcomes researcher will follow up with the participant for further screening and to schedule an interview.

2.2.2.3. Recording and Transcription

Interviews will be recorded and transcribed using an independent transcription agency. All information that could identify a participant, for example, if they state full name or address

during recorded interview, will be redacted from the transcript, so an anonymized version will be used for all analyses. These transcribed interviews will serve as units for analysis and qualitative coding.

2.2.3. Population and Sample Size

Adult participants on active study treatment in Study JZJB will be eligible to enroll in this addendum. Enrollment can occur at any time after baseline (Cycle 1). Additional informed consent will be required prior to completing a qualitative interview. Enrollment will be continued until conceptual saturation (as described in Section 2.3.2) has been reached; up to 40 interviews will be conducted if conceptual saturation is not reached with fewer interviews.

2.2.4. Conduct of Interviews

2.2.4.1. Schedule for Interview

Participants will be eligible for inclusion in the qualitative interview after they start study treatment and completed the FACT-GP5 on Day 1 of the first Cycle and have been consented by the site. Participants in JZJB who are exempt from completing PRO instruments will not be eligible for the qualitative interview. Participants who consent to participate in this study will be contacted by Modus Outcomes to schedule and conduct the interview. The ideal window for the interview is 10 to 14 weeks from start of treatment based on the FDA's recommendation for when peak toxicity can be accurately evaluated (session 2 of the 2020 FDA ASCO workshop; https://www.fda.gov/media/140370/download). However, the interview may occur at any time and will be conducted in the preferred language of the participant.

2.2.4.2. Interview Components

The semi-structured interviews will contain the following components:

- The concept elicitation section of the interviews will begin with open-ended questions. Participants will be encouraged to describe their experience in their own words. Targeted probes will be used to obtain specific information on concepts of interest after the participant has been given the opportunity to respond to the open-ended questions spontaneously.
- Cognitive debriefing will be conducted with the single-item FACT-GP5 instrument. Participants will be asked about the item's clarity and relevance, and their understanding and interpretation of the recall period and response options.
- Interpretation of high- versus low-side-effect bother will consist of participants describing the difference between each level of the response scale and which response level is tied to their perception of tolerability.

2.2.4.3. Pharmacovigilance

All interviewers will complete the sponsor's pharmacovigilance training prior to conducting participant interviews. Interviewers will determine whether AEs should be reported to sites or directly to the sponsor according to the sponsor's standards and procedures. Internal standard operating procedures at Modus Outcomes include senior review of AE forms and sign-off prior to reporting for quality assurance. The sponsor will supply an AE form to submit the documented patient report of a given event.

2.3. Analysis

2.3.1. Qualitative Analysis

For interviews conducted in a language other than English, transcripts will be translated into English. The transcripts will be analyzed thematically with inductive coding methods (Braun and Clarke 2006) using detailed line-by-line open and inductive coding (Bryman and Burgess 2002; Thomas 2006; Bowling 2009) with ATLAS.ti software using a general inductive approach (Thomas 2006). This means that, based on the content of the transcripts, relevant participant quotes will be assigned short codes, which will be used to organize the data. Coding will be tailored to the research objectives of the study: understanding the participant experience of AEs, and their understanding of the concepts of tolerability, bother, and burden. Independent parallel coding will be used to initiate the coding and ensure consistency using the first 2 transcripts. The lists of codes and associated quotes obtained by the independent coders will be compared for overlaps and inconsistencies. The coding will be revised as needed to reach coder agreement following the identification of new concepts in the remaining transcripts. A data dictionary will be developed and modified as necessary throughout the process and codes will be cleaned by a senior researcher. Codes will be inductively categorized based on coherent patterns into higher order conceptual domains forming a conceptual model using standard analytical techniques (Bryman and Burgess 2002; Bowling 2009; Klassen et al. 2009).

A codebook will be developed after the first 2 interviews are coded and will be modified as more codes are added. After each set of 5 interviews, the sponsor will conduct saturation analysis and will complete and discuss with the sponsor a table summarizing the way participants define bother, burden, and tolerability.

Table 1. Tracking Matrix: Concepts of Interest

Concepts of Interest	Code	Illustrative Patient Quotes	Underlying Symptomatic AEs or Impacts, as Described by Patient	Importance in Tolerability Perception (Ability or Desire to Adhere)
Bother	…	…	…	…
…	…	…	…	…
…	…	…	…	…
Burden	…	…	…	…
…	…	…	…	…
…	…	…	…	…
…	…	…	…	…
Tolerability				

Once coding is complete, findings from the interviews will be used to develop a conceptual framework of the participant experience of tolerability of treatment for thyroid cancer. The sponsor will ensure that the themes represented in the conceptual framework reflect the meaning of the data to provide an accurate representation of the participant experience of tolerability.

2.3.2. Saturation Analysis

A saturation analysis will be conducted to determine how much new information on the participant experience is obtained in each group of 5 interviews. The transcripts will be ordered chronologically, based on the interview completion dates, and then divided into groups of 5 transcripts. If important new concepts providing significant information regarding the components of side-effect burden/bother/tolerability arise in the last group, additional interviews will be considered to ensure all relevant concepts are elicited (principle of saturation). An example of a saturation table is provided below.

Table 2. Sample Saturation Table

Interviews	*1-5*	*6-10*	*11-15*	*16-20*	*21-25*	*25-30*
	New Concepts	*New Concepts*	*New Concepts*	*New Concepts*	*New Concepts*	*New Concepts*
	…	…	…	…	…	
	…	…	…	…		
	…	…	…			
	…	…	…			
	…	…				
	…					
	…					
	…					
	…					
	…					
New Concepts per Group	**10**	**5**	**4**	**2**	**1**	**0**

2.3.3. Cognitive Debriefing

For interviews conducted in a language other than English, transcripts will be translated into English. The transcripts will be analyzed for participant feedback on the FACT-GP5. Structured codes will be used to compile data on understanding of instructions (specifically impact of 7-day recall period on item completed daily), appropriateness, comprehensiveness and understanding of item content, interpretation of item response options, relevance of the response options, and participant's perspectives on the interpretation and relevance or meaningfulness of the thresholds between answer choices (most specifically between somewhat and quite a bit), and the participant opinion on where the threshold is for high-side-effect bother.

Table 3. Sample Cognitive Debriefing Summary Table

Relevance	**Clarity, Comprehension, and Interpretation**	**Retrieval of Information**	**Response Option Feedback**	**Meaning of Response Options**
Is the FACT-GP5 relevant to their experience of bother/burden/tolerability? Does it summarize the patient experience appropriately?	How do patients understand the item? Do they interpret as intended? (to be discussed since we need to clearly define what was intended)	What do patients consider when arriving at a response? (symptoms, impacts, timeframe, etc.)	Are response options appropriate for respondents?	Description of meaning and differences between all options.

Table 4. Participant Opinion on Threshold for High-Side-Effect Bother

Response Option at Which:	**A Little Bit**	**Somewhat**	**Quite a Bit**	**Very Much**
"high-side-effect bother" starts	n	n	n	n
They no longer consider current treatment "tolerable"[a]	n	n	n	n

Abbreviation: n = number

[a] Defined as "affects the ability or desire of the participant to adhere to the dose or intensity of therapy."

2.4. Reporting

A summary of the study findings will be compiled in a final report developed by Modus Outcomes. This report will include recommendations for how best to measure this concept and aid interpretation of the participant experience of tolerability with selpercatinib, cabozantinib, and vandetanib in MTC. Additionally, the anonymized transcripts will be provided to the sponsor. Provided that the recording does not contain any identifiable information, these recordings will be provided to the sponsor; however, any recordings that include information that required anonymization at the transcript level will not be shared with the sponsor.

2.5. General Information

2.5.1. Data Transfer, Management, and Storage

All personal data collected during this study will be de-identified according to Modus Outcomes' internal Quality Management System. If needed, de-identified data will be shared with the regulatory agency should they request such information.

Modus Outcomes uses an encrypted Citrix ShareFile server for data transfer from external parties and for storing all electronic project data. A specific folder will be created to upload or download the data that will be accessible only with a login and password, in compliance with regulatory guidance, for example, FDA, 21 CFR Part 11. Duplicate copies of electronic data are destroyed at the conclusion of the study. Master copies of all electronic data generated during the research study will be retained for 7 years after the conclusion of the study. After 7 years, these electronic data are destroyed using secure delete methods.

All analyses will be performed by trained and experienced Modus Outcomes personnel. Modus Outcomes' quality control process will be applied to ensure data integrity and accuracy of the results.

2.5.2. Ethical and Regulatory Considerations

2.5.2.1. Participant Data Protection

All participants will be assigned a separate, unique identifier, and computer-processed data will be identified by this unique identifier only, thereby ensuring that participants' identities remain unknown to the sponsor and cannot be linked to the primary clinical trial ID. As outlined in Section 2.1.4, no data that could identify a participant's identity will be provided to the sponsor.

2.5.2.2. Ethical Conduct of Study

The investigator and research personnel will conduct this study in accordance with ethical principles outlined in the Declaration of Helsinki. Research practices will be guided by Good Clinical Practice and regulatory requirements as applicable.

2.5.2.3. Risks and Benefits to Participants

This is a non-interventional plan. Participants will be informed that there is no specific health benefit to participation in these interviews; there is minimal risk posed to participants by participating in interviews. During or following concept elicitation and cognitive debriefing, participants may become more cognizant of aspects of their condition, including the symptoms and impacts of symptom severity they experience. This method of interviewing may cause

feelings of discomfort. Despite the efforts to protect participant privacy and to anonymize all data collection documents, there remains a potential risk of loss of participant confidentiality. Otherwise, there are no other risks of participation in these interviews. If participants have questions or concerns related to their condition or medical treatment, they will be encouraged to speak with their health care provider.

3. References

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4. Supporting Documentation

4.1 Appendix [10]: Participant Interview Guide

Introduction

Introduce yourself and the purpose of the study

Hello, my name is [Interviewer name] and I work for Modus Outcomes. Modus Outcomes is a company that talks to people about various health conditions. Currently, we are working with a pharmaceutical company to find out more about your experience in the LIBRETTO-531/JZJB trial.

Interview procedures

Today, you will have the opportunity to tell me about your experience in the trial, specifically about how you felt during the trial, including any side-effects you might have experienced and how they have affected you and your life. This discussion will last approximately 60 minutes. If you need to take a break or want to end the interview for any reason, you can do so at any time.

Before we start the discussion, I'd like to take a moment to describe how we will use the information you tell me today. As a participant in this trial, you've been asked to answer questions about how you feel and function on a "digital device" that looks like a cell phone or tablet. When we analyze and report the answers that all of the patients in this trial have sent us (you included), it's important that we do it in a way that's accurate. In other words, we want to get it right and report everyone's answers in a way that's true to your experiences. We're not going to ask you to think back and remember your answers you've sent, but we will take a look at one of the questions you've been asked so you can help us understand how patients like you answer and what you think about it.

I will start by asking you open-ended questions about your experience taking the cancer treatment you are receiving in the study, and may ask more specific questions later to make sure I understand what you mean. Then I will ask questions about some other topics, including how you think about side-effect burden or bother, and will ask for your feedback on one of the questions you have been asked in the trial.

There aren't any "right" or "wrong" answers to the questions I will ask you today. We are really interested in knowing about YOUR experience, so we appreciate anything you can tell us.

Audio recording

This interview will be audio recorded to make sure we capture all the information you share with us. Please try to speak clearly. If you need to take any breaks, please let me know. I can pause the recording at any time.

Anonymity and data handling

Recordings will be transcribed by an independent transcription agency. All information that could identify you will be left out of the transcriptions. These de-identified transcripts will be shared with the study sponsor and used in our analysis. Results of this interview will be anonymized, so no answers are attributable to any specific individual.

Adverse event reporting

During the interview, we will discuss your experience while taking the trial drug, including any side effects. We are required to report this to the company even if it has already been reported by you directly or by your physician to the company or the regulatory authorities. You will remain anonymous and only be identified by your participant ID number.

Closing

Do you have any questions for me before we begin?

Answer any questions that the participant may have. Ensure that they agree to have the interview recorded for the designated amount of time. Start the recording. State your name and the participant ID of the person you are interviewing along with the current date and time of the interview.

This is [Interviewer name] with participant [participant ID]. It is [date] at [time]. Do you agree to have this interview recorded?

Concept elicitation

Side effects from trial drug and impact on life

1. Can you begin by telling me how long have you been participating in the clinical trial?
2. Have you experienced any symptoms or side effects since you started the cancer treatment as part of this clinical trial? Can you tell me the different side-effects you've experienced?
    a. PROBE: [for each side effect] Can you describe what [side effect] was like?
    b. PROBE: [for each side effect] When did you first experience [side effect]?

c. PROBE: [for each side effect] How long did [side effect] last?
d. PROBE: [for each side effect] Did [side effect] tend to get better or worse day-to-day? How does it/did it get better or worse?
e. PROBE: [for each side effect] Did that side-effect bother you?
    i. As needed: How much did it bother you?
    ii. Why did it bother you?
f. PROBE: What was the impact of [each side effect] on your daily life?

3. Of the side-effects you've experienced since taking the treatment for this study, which bothered you the most? Which bothered you the least?
4. How have these side effects affected your daily life?
5. Can you tell me, in your own words, what "bothered by side-effects of treatment" means to you?
    a. When talking about side-effects, is there a difference between the word "bother" and the word "burden", or do they mean the same thing?

    [Note: if patient is unfamiliar with the term "burden," the following probes may be skipped.]

        i. Probe: How do you describe the difference between bother and burden?
        ii. Probe: If we were to ask you how all of the side-effects you're currently experiencing impact you, would you prefer me to use the word bother or burden?
6. If I were to ask you "do you think the study treatment you're taking is tolerable" what do you think of when answering?
    a. PROBE: What does the word tolerable mean to you?
    b. PROBE: Do you think "side-effect bother", as we discussed earlier, is related to tolerability?
    c. PROBE: Do you think "side-effect burden", as we discussed earlier is related to tolerability?
        i. What makes a cancer treatment tolerable?
        ii. What makes a cancer treatment not tolerable?
    d. At what point would you speak to your doctor about changing your treatment?
        i. PROBE: Does this vary according to the number of side-effects? (type/duration/severity?)

e. At what point would you speak to your doctor about stopping/discontinuing treatment?
    i. PROBE: Does this vary according to the number of side-effects? (type/duration/severity?)

[NOTE: if patient indicated a strong preference for bother or burden above, or does not know what one of the words means, only ask the applicable question here]

7. What is it like to have side effects over a long period of time that are bothersome/burdensome?
    a. How long is a "long time"?
    b. Are some side effects more or less bothersome/burdensome over time?
8. How do you tell the difference between symptoms of your cancer and side effects of treatment?
9. Did you discontinue study treatment earlier than planned?
    a. PROBE (if yes): Why?

Cognitive debriefing of the FACT-GP5

Initial debriefing of item

Direct the patient's attention to the FACT-GP5 and explain that we would like their feedback about this question - "Here is an image of a question you have been asked during the trial".

Instruct patient to read the question aloud and let them know that the interviewer will ask follow-up questions afterwards. Ask them to verbalize their thinking process and point out anything that seems vague, difficult to understand or to respond to, or not relevant to them.

Reassure the patient that we are looking for honest feedback on the item, and we hope to learn from them. There are no right or wrong things to say.

Inform the patient that follow-up questions will be asked to understand their perspective on the following:

- Clarity of instructions
- Format of question
- Item understanding, relevance, and interpretation
- Response option understanding, coverage, and consistency

1. What does this question mean to you in your own words?
    a. Is there anything unclear about this question? If yes, how would you ask the question to make it easier to understand?
2. When you have been asked this question during the study, what did you think about while answering?
3. What was it like for you to think back over the past 7 days while answering?

Response options and thresholds

In the question above, there are different answer choices. We call those "response options". I am going to ask you about each of those response options now.

1. Can you describe for each of the following response options:
    a. What it means in your own words?
    b. What it would mean if you chose that answer during the trial?
    c. How you would experience the side effect at each answer level?

    Not at all

    A little bit

    Somewhat

    Quite a bit

    Very much

2. Can you describe the difference between each category in your own words? Specifically, what would be different for you if you moved from one category to the next?
    a. Not at all to a little bit
    b. A little bit to somewhat
    c. Somewhat to quite a bit
    d. Quite a bit to very much
3. If you had to draw the line between two response options and on one side it meant "high side-effect bother" and on the other side it meant "not high side-effect bother" – where would that line be?
4. Thinking about cancer treatment in general, what side effect frequency/response option would be associated with you stopping treatment?
5. [if time remains] If you were asked this question about how much you were bothered by side-effects at the beginning of the trial, before you took the study treatment for the first time, how would you answer?

Closing

Opportunity for participant to share additional information

Those are all the questions I have for you today. Is there anything else you want to tell me about your experience in the clinical trial and side effects that would be important for researchers to know?

[Follow up as appropriate.]

Closing the interview

Thank you very much for helping us with this research. We appreciate your time and effort!

Conclude recording and close the interview.

10.8.6. Addendum 13.1 (Country-Specific Content for All Study Countries)

This addendum addresses protocol items to comply with local laws and regulatory requirements in all participating countries.

The following table describes the changes being made to Protocol JZJB.

Main Protocol Section # and Name	Description of Change
1.3.2. Screening, On-Study, and Post-Study Treatment Follow-Up Schedule of Activities for Patients on Arm A and Arm B	To provide clarification regarding the modality of imaging used for monitoring for premature growth plate closure
1.3.4. Optional Crossover Treatment (for patients crossing over from Arm B to Arm A)	To provide clarification regarding the modality of imaging used for monitoring for premature growth plate closure
8.2 Safety Assessments	Correction

Rationale for Addendum

The purpose of this addendum is to provide clarification regarding the modality of imaging used for monitoring for premature growth plate closure. For sites where the standard of care for this monitoring is bone age assessment, a radiograph of the hand will be used rather than MRI of the knee.

Protocol Additions

All deletions have been identified by ~~strikethroughs~~ and all additions have been identified by the use of underscores.

Section 1.3.2. Screening, On-Study, and Post-Study Treatment Follow-Up Schedule of Activities for Patients on Arm A and Arm B

Screening, On-Study, and Post-Study Treatment Follow-Up Schedule of Activities for Patients on Arm A and Arm B											
	Screening		**On-Treatment**				**Safety assessments prior to crossover**		**Post-Study Treatment**		
			Cycle = 28 days				**(only for patients on Arm B)**				
	(Day Relative to C1D1)		**Cycle 1**			**Cycle 2-n**	**V201[a]**		**Short-term Follow-up[a]**	**Long-term Follow-up[b]**	**Instructions**
			(±3 days)			(±3 days)	Day 1-30 (±7 days)	1-x days	(30 ± 7 days)	(90 ± 14 days)	
	≤42	**≤7**	**D1**	**D8**	**D15**	**D1**	**N/A**	**N/A**	**V801**	**V802-8XX**	
Procedure											
Growth plate imaging	X		See instructions								Only for patients <18 years of age who have not reached full adult height. ~~Knee MRI~~ Hand radiograph at baseline and every 6 months ±2 weeks). See Section 8.2.

Section 1.3.4. Optional Crossover Treatment (for patients crossing over from Arm B to Arm A)

Only applicable for patients initially randomized to Arm B (cabozantinib or vandetanib) who have progression that is confirmed by the BICR and who are eligible for crossover treatment.

Optional Crossover Treatment (for patients crossing over from Arm B to Arm A)								
	Crossover Screening	**On-Treatment**	**Post-Study Treatment**					
		Cycle = 28 days						
	Visit 300 (Day relative to start of treatment)	**Visit 301**	**Visit 302-n**	**Short-term Follow-up[a]**	**Long-term Follow-up[b]**	**Instructions**		
		Cycle 1	**Cycle 2-n**					
		(±3 days)	(±3 days)	(30 ± 7 days)	(90 ± 14 days)			
	≤42	**D1**	**D8**	**D15**	**D1**	**V801**	**V802-8XX**	
Procedure								
Growth plate imaging		See instructions			Only for patients <18 years of age who have not reached full adult height. ~~Knee MRI~~ Hand radiograph at baseline and every 6 months (±2 weeks). See Section 8.2.			

Section 8.2. Safety Assessments

Participants who have not yet obtained full adult height will undergo ~~MRI of one knee~~ radiograph of one hand at baseline and every 6 months while the growth plates remain patent. ~~Right knee is preferred, but~~ Whichever ~~knee~~ hand is imaged at baseline should be imaged at all time points.

Adolescents who have had a documented growth rate of <1 cm/year over the prior 2 years and/or have reached a midparental height of over 152 cm in girls and 167 cm in boys are likely to have obtained full adult height. If it is unclear that a patient has obtained full adult height, pretreatment ~~tibial~~ radiographs ~~(AP and lateral views)~~ of the ~~right knee~~ hand should be obtained and ~~MRI~~ further monitoring performed only if the growth plates remain patent. If the growth plates remain patent, the patient will have a ~~MRI~~ radiograph performed every 6 months until the growth plates are no longer patent.

10.9. Appendix 9: Abbreviations and Definitions

Term	Definition
abuse	Use of a study intervention for recreational purposes or to maintain an addiction or dependence
AE	adverse event: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
ALT	alanine aminotransferase
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
ATA	American Thyroid Association
ATP	adenosine triphosphate
authorized IMP	*Applicable to the EU only*: a medicinal product authorized in accordance with Regulation (EC) No 726/2004 or in any Member State concerned in accordance with Directive 2001/83/EC, irrespective of changes to the labelling of the medicinal product, which is used as an investigational medicinal product
blinding	A single-blind study is one in which the investigator and/or his staff are aware of the treatment but the participant is not, or vice versa, or when the sponsor is aware of the treatment but the investigator and/his staff and the participant are not. A double-blind study is one in which neither the participant nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the subjects are aware of the treatment received.
BICR	blinded independent central review
BID	twice daily
BOR	best overall response
BUN	Blood Urea Nitrogen
CAP	College of American Pathologists
CEA	carcinoembryonic antigen
cfDNA	circulating free DNA
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences

CLIA	Clinical Laboratory Improvement Amendments
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.
CONSORT	Consolidated Standards of Reporting Trials
cORR	confirmed ORR
CRF	case report form
CRP/CRS	clinical research physician/scientist: 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.
CSR	Clinical study report
Ct	calcitonin
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLTs	Dose limiting toxicities
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DOR	Duration of response
eCOA	electronic Clinical Outcome Assessment
ECOG	Eastern Cooperative Oncology Group
ECG	Electrocardiogram
EDC	electronic data capture system
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.
EORTC-IL 19	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 Version 3.0, item library 19
EQ-5D-5L	5-level-EuroQol

ER	Estrogen receptor
ERB	ethical review board
FACT-GP5	Functional Assessment of Cancer Therapy-Side Effects
FOIA	Freedom of Information Act
GCP	good clinical practice
GDPR	EU General Data Protection Regulation
GFR	Glomerular Filtration Rate
GLP	Good Laboratory Practices
GnRH	gonadotropin-releasing hormone
hERG	human ether-a-go-go
HIPPA	Health Insurance Portability and Accountability Act of 1996
HR	hazard ratio
IB	Investigator's Brochure
IC50	50% inhibitory concentration
ICF	informed consent form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
ILD	Interstitial Lung Disease
IMP	Investigational Medicinal Product (see also "investigational product") A medicinal product which is being tested or used as a reference, including as a placebo, in a clinical trial.
Informed consent	A process by which a participant voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the participant's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
interim analysis	An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created/locked.
IRB	Institutional Review Boards

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.
ISO/IEC	International Organization for Standardization/Independent Ethics Committee
ITT	intention to treat: The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a participant (that is, the planned treatment regimen) rather than the actual treatment given. It has the consequence that participant allocated to a treatment group should be followed up, assessed, and analyzed as members of that group irrespective of their compliance to the planned course of treatment.
IUD	intrauterine device
LHRH	luteinizing hormone-releasing hormone
LLT	Lower Level term
LTFU	long term follow-up
MedDRA	Medical Dictionary for Regulatory Activities
medication error	Errors in the prescribing, dispensing, or administration of a study intervention, regardless of whether or not the medication is administered to the participant or the error leads to an AE. Medication error generally involve a failure to uphold one or more of the 5 “rights” of medication use: the right participant, the right drug, the right dose, right route, at the right time. In addition to the core 5 rights, the following may also represent medication errors: • dose omission associated with an AE or a product complaint • dispensing or use of expired medication • use of medication past the recommended in-use date • dispensing or use of an improperly stored medication • use of an adulterated dosage form or administration technique inconsistent with the medication's labeling (for example, Summary of Product Characteristics, IB, local label, protocol), or • shared use of cartridges, prefilled pens, or both.
MHC-I	Major Histocompatibility Complex class I
misuse	Use of a study intervention for self-treatment that either is inconsistent with the prescribed dosing regimen, indication, or both, or is obtained without a prescription
MKIs	multikinase inhibitors
MRI	magnetic resonance imaging
MTC	medullary thyroid cancer

NCCN	National Comprehensive Cancer Network
NRS	numeric rating scale
NSCLC	non-small cell lung cancer
ORR	overall response rate
OS	overall survival
PD	progressive disease
PFS	progression free survival
PFS2	Progression free survival 2
PK	pharmacokinetics
PPIs	Protein pump inhibitors
PR	partial response
PRO	patient-reported outcomes
PTCs	papillary thyroid cancers
ORR	Overall response rate
OS	Overall survival
QD	once daily
QT	ECG interval measured from the onset of the QRS complex to the offset of the T wave
QTc	corrected QT interval
QTcF	QT interval corrected for heart rate using Fridericia's formula
QTcI	Corrected QT interval
RCC	Renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
RP2D	Recommended Phase 2 dose
RR	time between corresponding points on 2 consecutive R waves on ECG
RTK	receptor tyrosine kinase
SAE	serious adverse event

SAP	statistical analysis plan
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
SERD	selective estrogen receptor degraders
SERM	selective estrogen receptor modulators
SMD	Senior Management Designee
SoA	schedule of activities
SRS	stereotactic radiosurgery
SUSARs	suspected unexpected serious adverse reactions Refers to an adverse event that occurs in a clinical trial participant, which is assessed by the sponsor and or study investigator as being unexpected, serious, and as having a reasonable possibility of a causal relationship with the study intervention.
TEAE	Treatment-emergent adverse event: An untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment.
TTF	time-to-treatment failure
TFFS	treatment failure-free survival
TTNT	time to initiation of new anticancer therapy
UK	United Kingdom
ULN	upper limit of normal
WCLC	World Conference on Lung Cancer
WOCBP	woman of childbearing potential

10.10. Appendix 10: Protocol Amendment History

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

Amendment (h)

This amendment is considered to be nonsubstantial.

Overall Rationale for the Amendment:

The primary purpose of this amendment is to consolidate country-specific requirements into protocol appendix to meet EU CTR requirements. The changes are summarized in this table.

Section # and Name	Description of Change	Brief Rationale
10.8. Appendix 8: Country-Specific Requirements	Added an appendix to include EU-specific requirements for the following countries: 10.8.1. Addendum 3.1 (Germany) 10.8.2. Addendum 8 (Netherlands) 10.8.3. Addendum 10 (Czech Republic) 10.8.4. Addendum 11 (Belgium) 10.8.5. Addendum 12.2 (Czech Republic, Germany, Italy, Netherlands, Poland, Spain, Brazil, United States, United Kingdom, Australia, and Canada) 10.8.6. Addendum 13.1 (All Study Countries)	To consolidate country-specific requirements into protocol appendix to meet EU CTR requirements
Throughout	Minor editorial and formatting changes	Minor; therefore, not detailed

Amendment (g) (28 October 2022)

This amendment is considered to be nonsubstantial.

Overall Rationale for the Amendment:

In this amendment, the following changes are incorporated to provide a mechanism for dose modifications using 300-mg tablets for instances when vandetanib 100-mg tablets are not available.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis	In the Intervention Groups and Duration table: Updated cross-reference text to footnote [b].	For clarity.
6.1.1. Adult Dosing	In the Adult Dosing table: Updated cross-reference text to footnote [a].	For clarity.
6.6. Dose Modification	Added text and table outlining dose modification using 300-mg tablets.	Change made to provide a mechanism for dose modifications using 300-mg tablets for instances when vandetanib 100-mg tablets are not available.

Section # and Name	Description of Change	Brief Rationale
Throughout	Minor editorial and formatting changes.	Minor, therefore, not detailed.

Amendment [f]: (06 April 2022)

The amendment is considered to be substantial because it is likely to have a significant impact on the

- reliability and robustness of the data generated in the clinical study.

Overall Rationale for the Amendment:

In this amendment, the following changes are incorporated in response to fluctuating vandetanib availability:

Section # and Name	Description of Change	Brief Rationale
1.1. Synopsis	Added language regarding the switch from vandetanib to cabozantinib	Change incorporated in response to fluctuating vandetanib availability.
1.3. Schedule of Activities	Included a Control Arm Switch Table with title "Exceptional Control Arm Switch Treatment (for participants switching from vandetanib to cabozantinib)"	Change incorporated in response to fluctuating vandetanib availability, to ensure participants on control arm remain on active treatment.
1.3. Schedule of Activities	Assigned Level 3 section numbers (1.3.1, 1.3.2, 1.3.3, 1.3.4, and 1.3.5) to each SoA table	For clarification.
1.3. Schedule of Activities	In SoA table 1.3.2., in row "Vital signs (<18 years of age)", added that "Height should be measured every 6 months until they reach the age of 18."	For clarification.
1.3. Schedule of Activities	In SoA table 1.3.2., in row "Chemistry panel (<18 years of age)", added that 'Chemistry panel will be performed on adolescent participants every 4 weeks starting on Day 1 of Cycle 2-n and throughout."	Frequency of chemistry panel clarified for adolescents for consistency.
1.3. Schedule of Activities	In SoA table 1.3.4., in row "Vital signs (<18 years of age)", added that "Height should be obtained every 6 months until the age of 18."	For clarification.
1.3. Schedule of Activities	In SoA table 1.3.4., in row "Hematology (<18 years of age)", added that 'If testing is performed ≤7 days prior to C1D1, repeat testing does not need to occur on C1D1. See Appendix 2."	Frequency of hematology tests for adolescents clarified for consistency.
1.3. Schedule of Activities	In SoA table 1.3.4., in row "Chemistry panel (<18 years of age)", added that 'Chemistry panel will be performed on adolescent patients every 4 weeks starting Cycle 2-n and throughout."	Frequency of chemistry clarified for adolescents for consistency.
5.2.1. Eligibility Criteria for Crossover Treatment	Section title changed from "Enrollment Criteria for Crossover Treatment" to "Eligibility Criteria for Crossover Treatment"	For clarification, as participants who are crossing over are already enrolled to the study.

Section # and Name	Description of Change	Brief Rationale
	Updated the language of eligibility criteria for crossover	A minimum time window was added for the crossover, to allow for washout of control arm before the crossover to selpercatinib treatment.
6.1.3. Exceptional Switch from Vandetanib to Cabozantinib	Included this new section to add the language for switching	Change incorporated in response to fluctuating vandetanib availability to ensure participants on control arm remain on active treatment.
6.1.3.1. Eligibility Criteria for Switching from Vandetanib to Cabozantinib	Included this new section to add eligibility criteria for switch from vandetanib to cabozantinib	Change incorporated in response to fluctuating vandetanib availability to ensure participants on control arm remain on active treatment.
8. Study Assessments and Procedures	Added language regarding safety assessments	Based on feedback from investigators and that if clinically indicated, more frequent assessments may be required in certain cases.
10.2. Appendix 2: Clinical Laboratory Tests	Added method for screening for protein in urine of participants	Based on feedback from sites and investigators, specifically if urine dipstick is used and result is positive, then a urine sample should be sent for urinalysis.
Throughout	Minor editorial and formatting changes	Minor, therefore, not detailed.

Amendment (e)

The amendment is considered to be substantial because it is likely to have a significant impact on the

- scientific value of the trial
- conduct or management of the trial

Overall Rationale for the Amendment:

In this amendment, the following changes are incorporated in response to,

- Regulatory feedback
    - Added progression free survival (PFS), as a primary endpoint and removed it as a secondary endpoint
    - Removed treatment failure free survival (TFFS), as a primary endpoint and added it as a secondary endpoint
- New external data disclosure: The study has been updated to an adaptive design to allow sample size re-estimation based on results at an interim analysis
- Site feedback: Updated the cycles to align the visits with the schedule

The remainder of changes include correction of errors from amendment (d) and to incorporate feedback from Ethics Committee/Institutional Review Boards and investigators to improve the conduct of the study.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis, 3. Objectives and Endpoints, 4.1. Overall Design	Removed treatment failure free survival (TFFS), as a primary endpoint and added it as a secondary endpoint Added progression free survival (PFS), as a primary endpoint and removed it as a secondary endpoint	Based on regulatory agency feedback
1.1 Synopsis, 4.1. Overall Design Number of Participants	Number of participants revised to 250-400	Change to adaptive study design and sample size re-estimation
1.1 Synopsis Intervention Groups and Duration	Revised footnote a to include reduced starting dose of vandetanib in adolescent patients with moderate renal impairment Revised footnote b to add the term 'adult'	Based on local clinical feedback
1.2 Schema	Number of participants revised to 250-400 Removed measurable disease by RECIST 1.1 Removed treatment failure Removed separate number of participants from Arm A and Arm B	Change to adaptive study design
1.3 Schedule of Activities (SoA)	Addition of AE collection to the Pre-screening SoA	To maintain internal document consistency
1.3 Schedule of Activities (SoA)	In the instructions throughout, Cycles 2-14 is updated to Cycles 2-16 and Cycles 14, 17, 20 are updated to 16, 19, 22, etc.	To align the visits with the schedule
1.3 Schedule of Activities (SoA)	Updated instructions for ECG procedure to include additional ECG at C16D1	To align subsequent ECGs with onsite clinical visit schedule
1.3 Schedule of Activities (SoA)	Updated instructions for Phone visit procedure with online clinical visit timepoints Updated the cycles after which a phone follow-up visit will occur at every non-clinical visit	To align the visits with the schedule and for clarification
1.3 Schedule of Activities (SoA)	Added hematology procedure for participants ≥18 years of age and <18 years of age at Screening at ≤42 day and removed from ≤7 day	Clarification for sites
1.3 Schedule of Activities (SoA)	Added chemistry panel procedure for participants ≥18 years of age and <18 years of age at Screening at ≤42 day and removed from ≤7 day	Clarification for sites

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities (SoA)	Added 28 days for radiologic imaging procedure at Screening (≤42 day) Removed initiation of other anti-cancer therapy in instructions for radiologic imaging	Clarification for sites and based on regulatory agency feedback
1.3 Schedule of Activities (SoA)	Updated instructions for HRQoL and Health Status (EQ-5D-5L) procedures from "After completion of 1 year of treatment" to "Starting with C16"	To align the visits with the schedule
1.3 Schedule of Activities (SoA)	Updated instructions for Plasma for cfDNA collection	Clarification for sites
2.3 Benefit/Risk Assessment	Revised safety profile of selpercatinib	Correction and clarification
3 Objectives and Endpoints	Added safety assessment per (CTCAE) v5.0 of selpercatinib in patients assigned to Arm B who crossover to selpercatinib after progression in exploratory objectives and endpoints	Based on local clinical feedback
4.1 Overall Design	Revised the patient enrollment data and updated the section with change in primary endpoint and key secondary endpoint.	Change to adaptive study design
4.2 Scientific Rationale for Study Design	Updated the section with change in primary endpoint and key secondary endpoint. Rationale for another key secondary endpoint, comparative tolerability has been added Added rationale for adaptive design	Based on regulatory agency feedback
4.4 End of Study Definition	Added total study duration	Based on regulatory agency feedback
5.1 Inclusion Criteria	Revised Inclusion Criterion 2	Clarification for sites
	Clarified Inclusion Criterion 9	Requirement for treatment with Vandetanib
5.2 Exclusion Criteria	Added Inclusion Criterion 2b as a reference to Exclusion Criterion 22	Clarification for sites
5.2.1 Enrollment Criteria for Crossover Treatment	Clarified exceptions to be made or not for participants to crossover to selpercatinib based on eligibility criteria	Based on local clinical feedback
6.1 Study Intervention(s) Administered	Clarified that cycles should not be delayed for AEs. Cycle 13 was updated to Cycle 15	Clarification for sites
6.1.1 Adult dosing	Added footnote a to adult dose of Arm B2 and removed it from intervention Arm B2 Added footnote a in the table for Vandetanib dosing nomogram for adolescent participants	Clarification for sites

Section # and Name	Description of Change	Brief Rationale
6.3 Measures to Minimize Bias: Randomization and Blinding	Updated to include evaluation of aggregate interim efficacy results and safety data. Added measures to maintain trial integrity after the sample size re-estimation to avoid disclosure of the interim results	Based on regulatory agency feedback
6.6 Dose Modification	Updated the table title for Vandetanib general dose reductions for treatment related toxicities to include starting dose for moderate renal impairment for adolescent participants	Clarification for sites
6.6.2 Dose Modifications for Selpercatinib Related Liver Test Abnormalities	Added CTCAE version 5.0 with slight modification as a reference for grading liver test abnormalities	Based on local clinical feedback
6.6.3 Dose Modifications for Thrombocytopenia	Added "if thrombocytopenia is determined to be related to selpercatinib" for patient upon recovery to Grade 1 or better, the patient should resume selpercatinib at a reduced dose of one dose level reduction	Based on local clinical feedback
7.1 Discontinuation of Study Intervention	Updated the disease progression circumstance with expectations for procedures for each participant	Clarification for sites
8.1.1 Imaging 8.1.2 BICR Assessment	Removed initiation of new anticancer therapy as part of radiographic disease progression assessment for patients who discontinue treatment without radiographic progression by BICR	Based on regulatory agency feedback
8.3 Adverse Events and Serious Adverse Events	Added CTCAE version 5.0 with slight modification as a reference for post baseline grading for all laboratory values Added SAE reporting guidance after signing the prescreening ICF and the main study ICF	Clarification for sites
8.5 Pharmacokinetics	Updated collection of blood for PK assessment	Clarification for sites
8.9.4 PRO-CTCAE	Updated information that the PRO-CTCAE will not be available to the patient or onsite clinicians for clinical patient management	Clarification for sites
9.1 Statistical Hypothesis	Removed TFFS and added PFS evaluation for treatment of patients	Based on regulatory agency feedback
9.2 Sample Size Determination	Revised the section to include adaptive study design and sample size re-estimation based on PFS.	Change to adaptive study design

Section # and Name	Description of Change	Brief Rationale
9.3 Populations for Analyses	Added crossover and tolerability evaluable populations and their respective descriptions	Based on regulatory agency feedback and to maintain consistency
9.4.3.1 Primary Analyses	Added PFS as primary analysis. Removed TFFS as primary analysis	Based on regulatory agency feedback
9.4.3.2.1 Treatment Failure Free Survival	Added TFFS as a key secondary analysis	Based on regulatory agency feedback
9.4.3.2.2 Comparative Tolerability	Added comparative tolerability as another key secondary analysis	Based on regulatory agency feedback
9.4.3.2.3 Overall Survival	Updated OS analysis	Change according to adaptive study design
9.4.3.3 Other Secondary Analyses	Updated language for secondary outcomes assessment based on changes made to the primary and key secondary analyses	Based on regulatory agency feedback and to maintain consistency
9.4.3.5 Tertiary/Exploratory	Added PFS after crossover as an endpoint	Based on regulatory agency feedback
9.4.4 Safety Analyses	Added details for safety data after crossover	Based on local clinical feedback
9.5 Interim Analyses	Added the trigger for interim analyses and guidance for the study results categorization at interim analysis Removed TFFS interim analysis	Based on regulatory agency feedback and to maintain consistency. Change to adaptive study design
10.2. Appendix 2: Clinical Laboratory Tests	Removed the exception for adult patients not requiring a visit concurrently with labs from local laboratory results	Correction and clarification
10.2. Appendix 2: Clinical Laboratory Tests	Added assessments performed remotely/virtually for requirement of local laboratory results. Standard of care language updated for Triiodothyronine (T3) and Thyroxine (T4)	Clarification for sites
10.4. Appendix 4: Liver Safety: Suggested Actions and Follow-up Assessments	Added language for tests to be done at occurrence of Grade ≥3 elevated hepatic lab increases (ALT, AST, or direct bilirubin)	Clarification for sites
10.6. Appendix 6: *RET* activating mutations in MTC	Removed Y791F/N	Based on latest scientific evidence
10.7. Appendix 7: Restricted and Prohibited Concomitant Medications	Revised the reference for a current list of agents known to cause QTc prolongation	Editorial consistency
11. References	Added cited guidance documents	Editorial consistency.

Section # and Name	Description of Change	Brief Rationale
Throughout	Minor editorial and formatting changes	Minor, therefore, not detailed

Amendment (d)

This amendment is considered to be substantial 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:

The primary rationale for this amendment was to update information around the comparative tolerability key secondary objective based on regulatory agency feedback. Changes from additional regulatory and investigator feedback and minor corrections are also incorporated.

Section # and Name	Description of Change	Brief Rationale
Section 1.1. Synopsis, Section 3. Objectives and Endpoints	Added language related to secondary endpoint of comparative tolerability	Clarification based on regulatory agency feedback
Section 4.1 Overall Design	Added language about the secondary endpoint of comparative tolerability	Clarification based on regulatory agency feedback
Section 1.1. Synopsis	Removed footnote b below the Intervention Groups and Duration table	Correction
Section 1.2. Schema	Updated schema with minor changes	Corrections
Section 1.3. Schedule of Activities (SoA)	Added language to the prescreening ICF for *RET* testing row in the prescreening SoA	To provide flexibility to patients in prescreening
Section 1.3. Schedule of Activities (SoA)	Added a row for prescreening ICF for radiologic imaging submission for BICR review	To provide flexibility to patients in prescreening
Section 1.3 Schedule of Activities (SoA)	Added a row for demographic information in the prescreening SoA and the screening, on-study, and post-study treatment follow-up SoA for patients on Arm A and Arm B	Clarification
Section 1.3 Schedule of Activities (SoA)	Removed C1 D22, C2-n D8, C2-n D15 and C2-n D22 from the screening, on-study, and post-study treatment follow-up SoA for patients on Arm A and Arm B and the optional crossover treatment SoA	No sample collection at these visits

Section # and Name	Description of Change	Brief Rationale
Section 1.3. Schedule of Activities (SoA)	Increased screening duration from ≤28 to ≤42 days	To account for additional time needed to arrange imaging, imaging review, RET review, etc.
Section 1.3. Schedule of Activities (SoA)	Added coagulation sample to be collected at short-term follow-up visit	Correction
Section 1.3. Schedule of Activities (SoA)	Clarified instructions on when to collect certain measurements and perform specific tests	Following standard of care for changes to collection of chemistry panel; Clarification for remainder of changes
Section 1.3. Schedule of Activities (SoA)	Added a row for chemistry panel (<18 years of age)	Clarification
Section 1.3. Schedule of Activities (SoA)	Added a sentence about information on suggested modalities being found in Section 8.1	Clarification
Section 1.3. Schedule of Activities (SoA)	Changed language stating that repeated submission of scans greater than 10 business days after date of collection will be considered a protocol deviation	Correction
Section 1.3. Schedule of Activities (SoA); Section 8.9.1. Patient-Reported Outcomes	Added a statement restricting collection of Bristol Stool Form Scale, bowel movement frequency, and worst pain NRS to 1 year in both the main and crossover SoAs	Based on regulatory agency feedback
Section 1.3. Schedule of Activities (SoA)	Corrected sample collection for HRQoL (EORTC-QLQ-C30) and Health status (EQ-5D-5L)	Correction
Section 1.3. Schedule of Activities (SoA)	Removed language related to sample usage in the archived tumor tissue or fresh biopsy row	Correction
Section 1.3. Schedule of Activities (SoA)	Removed 'analysis and exploratory biomarkers' from Plasma for cfDNA row	Clarification
Section 1.3. Schedule of Activities (SoA)	Added collection times for Plasma for cfDNA	Clarification
Section 2.2.1. Selpercatinib	Added a sentence to reflect interim analysis data	Updated to reflect new data
Section 5.1. Inclusion Criteria	Amended Inclusion Criterion 2 to address inclusion of patients with mixed histology	Updated to align with clinical standard practice
Section 5.1. Inclusion Criteria	Amended Inclusion Criterion 3 to specify eligibility based on evaluable disease	Updated to align with clinical standard practice
Section 5.1. Inclusion Criteria	Amended Inclusion Criterion 4 requirements for germline assays	Clarification
Section 5.1. Inclusion Criteria	Amended Inclusion Criterion 7 to specify and/or amend length of time prior to first treatment dose	Updated for consistency with drug labels

Section # and Name	Description of Change	Brief Rationale
Section 5.1. Inclusion Criteria	Amended Inclusion Criterion 10 to reduce use of the highly effective contraceptive method from 6 to 4 months following the last dose of study drug	Updated for consistency with comparator drug labels
Section 5.1. Inclusion Criteria	Removed sentence regarding condom usage from Inclusion Criterion 10	Based on regulatory agency feedback
Section 5.2. Exclusion Criteria	Amended Exclusion Criterion 15 language for QT changes, and added language for patients with bundle branch block	Clarification
Section 5.2. Exclusion Criteria	Amended Exclusion Criterion 21 to remove references to cervical carcinoma in situ	Updated to align with clinical standard practice
Section 5.2. Exclusion Criteria	Amended Exclusion Criterion 26 to specify drug name	Based on regulatory agency feedback
Section 5.4. Screen Failures	Removed restriction for number of times a participant may be rescreened	Clarification/no medical justification for prior restriction
Section 6.5. Concomitant Therapy	Added language related to exercising caution when a P-gp substrate, MATE1 substrate, or BCRP substrate is co-administered with selpercatinib	Based on regulatory agency feedback
Section 6.5.1. CYP3A4 Inducers or Inhibitors	Added guidance about co-administration of selpercatinib with sensitive CYP3A4 substrates	Based on regulatory agency feedback
Section 6.6. Dose Modification	Moved up language related to permanent discontinuation from later in the section	Based on regulatory agency feedback
Section 6.6. Dose Modification	Added language addressing study treatment continuation in the case of hypertension	Updated to align with clinical standard practice
Section 6.6. Dose Modification	Changed timing related to omission of treatment for drug-related toxicities from >28 days to >42 days	To provide additional time to patients for recovery from toxicities
Section 6.6. Dose Modification; Section 8.2.1. Electrocardiograms	Moved toxicity language related to prolongation of the ECG QTc interval as a result of vandetanib dosing to Section 8.2.1	Redundant; moved from Section 6.6. to Section 8.2.1. to have all ECG dose adjustment information in one place
Section 6.6.2. Dose Modifications for Selpercatinib Related Liver Test Abnormalities	Specified pertinent hepatic labs described (ALT, AST, or direct bilirubin)	Clarification
Section 6.6.3. Dose Modifications for Thrombocytopenia	Modified language to address resumption of selpercatinib after a thrombocytopenia event	Updated to align with clinical standard practice
Section 8.1.1. Imaging	Amended language to clarify all imaging is required	Clarification

Section # and Name	Description of Change	Brief Rationale
Section 8.1.1. Imaging	Added language for imaging guidance	Updated to align with clinical standard practice
Section 8.1.1. Imaging	Added information on suggested imaging modalities	Clarification
Section 8.2.1. Electrocardiograms	Specified QTcF greater than 500 msec is a Grade 3 prolongation per CTCAE	Clarification
Section 8.2.1. Electrocardiograms	Added language related to dose adjustment requirements for an alternative cause	Clarification
Section 8.5. Pharmacokinetics	Added a sentence related to additional sample collection in patients experiencing selpercatinib-related drug hypersensitivity	Clarification
Section 8.8.1. Samples Required for Eligibility	Amended timing of sponsor approval prior when fewer slides are collected than requested	Clarification
Section 9.3. Populations for Analyses	Removed language related to safety data	Clarification
Section 9.4.3.1. Primary Analyses	Added sentence and censoring details related to independent review. Amended censoring rules for TFFS	Clarification based on Ethical Review Board feedback
Section 9.4.3.2. Secondary Analyses	Changed hierarchy of secondary endpoints	Clarification
Section 9.4.3.2. Secondary Analyses	Added definition of progression-free survival assessed by BICR	Clarification
Section 9.4.3.2. Secondary Analyses	Added definition of TFFS per investigator assessment	Clarification
Section 9.4.3.2. Secondary Analyses	Deleted reference to cfDNA	Correction
Section 9.4.3.2. Secondary Analyses	Added definition of comparative tolerability	Clarification based on regulatory agency feedback
Section 9.4.7.1.1. Patient Reporting Outcomes (PROs)	Removed description related to time to event analyses	Clarification based on regulatory agency feedback
Section 9.5. Interim Analyses	Moved and amended language related to early stopping for PFS and TFFS	Clarification based on regulatory agency feedback
Section 9.5. Interim Analyses	Added details about comparative tolerability testing	Clarification based on regulatory agency feedback
Appendix 2: Clinical Laboratory Tests	Removed unnecessary testing components	Correction
Appendix 4: Liver Safety: Suggested Actions and Follow-up Assessments	Changed local to central laboratory in footnote a	Clarification

Section # and Name	Description of Change	Brief Rationale
Appendix 7: Restricted and Prohibited Concomitant Medications	Removed Aprepitant from the list of moderate inhibitors	Correction
Throughout the protocol	Minor formatting and editorial changes	Minor, therefore not detailed

Amendment (c)

This amendment is considered to be substantial 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:

There are two major changes within amendment (c):

- Changing of the criteria of events counted toward the primary endpoint of treatment failure free survival (TFFS), and
- Aligning the required visit schedule and procedures to better align with standard of care treatment with prolonged use of oral kinase inhibitors.

The previous criteria for including intolerable events to be considered in TFFS was considered to be too narrow, and the new wording better incorporates treatment-emergent adverse events (TEAEs) that may require immediate discontinuation of study treatment. The timing between study visits and most study procedures is lengthened to 12 weeks (from 4 weeks) for adult patients who remain on treatment for greater than 1 year.

The remainder of changes include new information from the latest version of the Investigator's Brochure (IB), correct errors from amendment (b), and incorporate feedback from Ethics Committee/Institutional Review Boards and investigators to improve the conduct of the study.

Section # and Name	Description of Change	Brief Rationale
Section 1.1. Synopsis (Rationale) Section 2.2. Background	Changed prevalence of *RET* gene mutations accounting for MTC	Correction
Section 1.1. Synopsis (Objectives and Endpoints) Section 3. Objectives and Endpoints	Removed PRO-CTCAE as a secondary endpoint, added it as an exploratory endpoint	Change in study design; Clarification
Section 1.1. Synopsis (Objectives and Endpoints) Section 3. Objectives and Endpoints	Changed secondary objective related to PK	Clarification
Schedule 1.3. Schedule of Activities	Separated pre-screening SoA from screening, on-study and post-treatment follow-up SoA for Patients on Arm A and B	Clarification
Schedule 1.3. Schedule of Activities	Updated short-term and long-term follow-up visit ranges in both the Screening, On-Study, and Post-Study Treatment Follow-Up SoA as well as the optional crossover treatment SoA	Clarification
Schedule 1.3. Schedule of Activities	Clarified collection schedules for physical examination, vital signs, ECOG PS, hematology, urine protein, calcitonin, CEA, patient diary, HRQoL (EORTC QLQ-C30), Health Status (EQ-5D-5L) and plasma for cfDNA analysis and exploratory biomarkers in both the Screening, On-Study, and Post-Study Treatment Follow-Up SoA as well as the optional crossover treatment SoA	Align with changes in visit frequency
Section 1.3. Schedule of Activities	Added a phone visit for the collection of concomitant medications, AEs, labs, and patient dosing diary in both the Screening, On-Study, and Post-Study Treatment Follow-Up SoA as well as the optional crossover treatment SoA	Support changes in visit frequency
Section 1.3. Schedule of Activities	Added a range to collection window for Tanner staging and growth plant monitoring in both the Screening, On-Study, and Post-Study Treatment Follow-Up SoA as well as the optional crossover treatment SoA	Clarification
Section 1.3. Schedule of Activities	Updated serum cortisol and ACTH language; removed 24-hour urine for free cortisol collection and language in both the Screening, On-Study, and Post-Study Treatment Follow-Up SoA as well as the optional crossover treatment SoA	Removed unnecessary procedure

Section # and Name	Description of Change	Brief Rationale
Section 1.3. Schedule of Activities	Added rows and instructions for specific adolescent patient procedures in both the Screening, On-Study, and Post-Study Treatment Follow-Up SoA as well as the optional crossover treatment SoA	Clarification associated with change in visit frequency for adult patients
Schedule 1.3. Schedule of Activities	Changed collection window for ECG measurement in both the Screening, On-Study, and Post-Study Treatment Follow-Up SoA as well as the optional crossover treatment SoA	Change in guidance in IB
Schedule 1.3. Schedule of Activities	Clarified testing expectations for pregnancy testing in both the Screening, On-Study, and Post-Study Treatment Follow-Up SoA as well as the optional crossover treatment SoA	Clarification
Schedule 1.3. Schedule of Activities	Updated specifications related to performance and submission of results of radiologic scans in both the Screening, On-Study, and Post-Study Treatment Follow-Up SoA as well as the optional crossover treatment SoA	Clarification
Schedule 1.3. Schedule of Activities	Updated language related to collection of Bristol Stool Form scale and bowel movement frequency, worst pain NRS, pro-CTCAE, FACT-GP5, EORTC IL 19 in both the Screening, On-Study, and Post-Study Treatment Follow-Up SoA as well as the optional crossover treatment SoA	Clarification
Schedule 1.3. Schedule of Activities	Increased pre-dose blood draw window for blood samples for pharmacokinetics in both the Screening, On-Study, and Post-Study Treatment Follow-Up SoA as well as the optional crossover treatment SoA	Facilitate single lab collection for relevant visits
Schedule 1.3. Schedule of Activities	Updated archived tumor or fresh biopsy and optional post-progression tumor biopsy collection instructions in the Screening, On-Study, and Post-Study Treatment Follow-Up SoA	Clarification
Section 3. Objectives and Endpoints	Amended type of DNA sample in exploratory objective related to *RET* mutation status	Clarification
Section 5.1. Inclusion Criteria	Clarified language for histological diagnosis in Inclusion Criterion 2	Clarification
Section 5.1. Inclusion Criteria	Updated *RET* alteration analysis description in Inclusion Criterion 4	Clarification
Section 5.1. Inclusion Criteria	Removed sentence related to archived tumor tissue requirements in Inclusion Criterion 4	Removed duplicate language

Section # and Name	Description of Change	Brief Rationale
Section 5.2. Exclusion Criteria Medical Conditions	Updated gene mutations and fusions in Exclusion Criterion 13	Updated for clinical relevance in MTC
Section 6.1. Study Intervention(s) Administered	Updated cycle instructions for AEs	Clarification
Section 6.1. Study Intervention(s) Administered	Added clarification related to drug dispensation	Clarification
Section 6.1.2. Adolescent Dosing	Updated language around BSA-adjusted dosing of selpercatinib	Clarification
Section 6.1.2. Adolescent Dosing	Removed dose increase guidance column related to vandetanib dosing and updated BSA dose column for selpercatinib	Correction of erroneously included information
Section 6.5. Concomitant Therapy	Updated prior concomitant therapy language and added surgery or RT permissions	Detail added for needed clarity
Section 6.5.2. Agents that alter gastric acidity (PPIs and H2 blockers)	Amended language related to concomitant use of PPIs	New data resulted in updated guidance
Section 6.6. Dose Modification	Updated definition for Intolerable AEs Added guidance related to additional dose adjustments for AEs that are resolved following a dose reduction	Clarification/Modification
Section 6.6. Dose Modification	Addition of severe/life-threatening hemorrhage as a criterion for permanent discontinuation in patients receiving selpercatinib	For consistency with updated IB
Section 6.6. Dose Modification	Added definition for intolerable AEs Amended guidance related to general dose level reductions	For consistency with updated IB
Section 6.6.1. Dose Modifications for Selpercatinib Hypersensitivity	Removed recommended lab testing for selpercatinib drug hypersensitivity	For consistency with updated IB
Section 6.6.2. Dose Modifications for Selpercatinib Related Liver Test Abnormalities	Updated dose modification guidelines for selpercatinib related liver test abnormalities	For consistency with updated IB
Section 6.6.3. Dose Modifications for Thrombocytopenia	Updated dose modification guidelines; Removed sponsor notification instructions	For consistency with updated IB
Section 8.1.1. Imaging	Clarified assessment instructions for patients who discontinue treatment without radiographic progression by BICR Clarified scan interval schedule	Clarification
Section 8.1.2. BICR Assessment	Added clarification that the required actions are regarding imaging which needs collection and submission, but not	Clarification

Section # and Name	Description of Change	Brief Rationale
	regarding post discontinuation imaging without requirement of submission.	
Section 8.5. Pharmacokinetics	Updated PK sample draw language (in relation to dosing)	Clarification
Section 8.8.2. Biomarkers	Added language related to whole blood collection Added language to account for gene testing other than *RET*	Clarification
Section 8.9.1. Patient-reported Outcomes	Modified language regarding use of electronic questionnaires	Clarification and correction
Section 9.2. Sample Size Determination	Corrected OS percentages	Correction of error
Section 9.4.3.1 Primary Analyses	Clarified study drug related AE qualifications	Clarification
Section 9.4.3.1 Primary Analyses	Added a sentence describing TFFS determination by an independent review committee	Clarification
Section 9.4.3.2 Secondary Analyses	Added clarification of censoring rules for PFS2	Clarification
Section 10.1.9. Provisions for Changes in Study Conduct During Emergencies	Added details related to emergency mitigation	Risk mitigation for patients during an emergency.
Section 10.2. Appendix 2 Clinical and Laboratory Tests	Added clarification related to exception for local testing Updated cortisol and urine pregnancy test language	Clarification
Section 10.6. Appendix 6: *RET* activating mutations in MTC	Amended list of genes that are known driver alterations in MTC	Specify appropriate eligible population
Section 10.7. Appendix 7 Restricted and Prohibited Concomitant Medications	Updated language around CYP inhibitors	Not updated in Amendment b
Section 10.7. Appendix 7 Restricted and Prohibited Concomitant Medications	Removed guidance related to timeframe of PPI usage and PPI instructions	Not updated in Amendment b
Throughout the protocol	Minor formatting and editorial changes	Minor, therefore not detailed

Amendment [b]: (18 November 2019)

This amendment is considered to be substantial 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:

In the original protocol version, the starting dose of the control arm treatment vandetanib for patients with mild to moderate renal impairment was not included. In this amendment, the starting dose for these patients is incorporated, in order to maximize patient safety. Other clarifications and corrections are included as outlined below.

Section # and Name	Description of Change	Brief Rationale
5.1 Inclusion Criteria	Added text for unstained, archived tumor tissue in Inclusion Criterion 4.	Based on regulatory agency feedback.
1.1 Synopsis; 3 Objectives and Endpoints	A secondary objective was added.	To assess/evaluate performance of local *RET* laboratory tests compared to a single, central test.
1.1 Synopsis; 3 Objectives and Endpoints	A secondary objective was added.	To assess the PK of selpercatinib in the patient population.
6.1 Study Intervention(s) Administered	Replaced text for the starting dose of vandetanib for patients with moderate renal impairment.	Per vandetanib label, patients with moderate renal impairment should begin treatment at a dose of 200 mg.
1.1 Synopsis	Added text for starting dose of vandetanib for patients with moderate renal impairment.	Per vandetanib label, patients with moderate renal impairment should begin treatment at a dose of 200 mg.
9.4.5 Pharmacokinetic/Pharmacodynamic Analyses	Updated text to include a plan for conducting population PK and exposure-response analyses.	Selpercatinib plasma concentrations will be summarized by descriptive statistics and graphics. Additionally, the data will be evaluated through population PK methodology.
4.1 Overall Design	Further clarified physician's choice language.	Clarification for sites.
1.1 Synopsis; 4.1 Overall Design	Removed geographic region stratification factor.	No expected difference in outcomes based on geographic region.
1.3 Schedule of Activities	Removed tobacco and alcohol use.	The medical history does not include tobacco and alcohol use.
1.3 Schedule of Activities	Updated text about sample collection.	Based on regulatory agency feedback.

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities	Removed Pregnancy Test LTFU Instructions.	Pregnancy Test not needed in LTFU.
1.3 Schedule of Activities	Added ECGs every 3 months after Cycle 8 for participants receiving selpercatinib.	Clarification
1.3 Schedule of Activities	Clarified language for survival and PFS2 assessment.	Clarification
1.3 Schedule of Activities	Updated collection for Plasma for cfDNA analysis and exploratory biomarkers.	Clarification
1.3 Schedule of Activities	Added cortisol, ACTH, 24-hour urine for free cortisol for short term follow up.	Inadvertently deleted.
5.2 Exclusion Criteria	Clarified exclusion in Exclusion Criterion 16.	Based on regulatory feedback.
5.2 Exclusion Criteria; 6.5 Concomitant Therapy; 6.5.1 CYP3A4 Inducers or Inhibitors; 6.5.2 Agents That Alter Gastric Acidity (PPIs and H2 blockers); Appendix 7 Restricted Concomitant Medications	Removed prohibition on CYP3A4 and PPI concomitant medications in Exclusion Criterion 23 and 24 and throughout.	Based on updated information.
5.2 Exclusion Criteria	Added exception for participants with MEN2-associated pheochromocytoma in Exclusion Criterion 21.	Based on feedback.
Throughout	Updated the name for EORTC-QLQ30-C30-PF.	Clarification.
Throughout	Updated the name for LOXO-292 to selpercatinib.	Clarification.
Section 9.2 Sample Size Determination	Removed sentence for increasing sample size consideration.	Based on regulatory agency feedback.
9.4.3.2 Secondary Analyses	Removed CNS ORR.	Inadvertently included in original protocol.
8.2.1 Electrocardiograms	Added text about ECG.	Added for patient safety.

Section # and Name	Description of Change	Brief Rationale
8.8 Biomarkers	Updated text about sample collection and split section into two subsections.	Based on regulatory agency feedback.
9.4.3.2.1 *RET*-Testing Concordance Analysis	Added subsection regarding concordance analysis.	Based on regulatory agency response on *RET* testing, concordance between *RET*-testing results based on local laboratory tests and centrally assessed results will be evaluated.
Appendix 7 Restricted Concomitant Medications	Added examples of H2 blocking agents.	Clarification for sites.

Amendment [a]: (12 November 2019)

This amendment is considered to be substantial 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:

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis, 1.2 Schema, 4.1 Overall Design, 6.1 Study Intervention(s) Administered; 6.6 Dose Modification	Adolescent dose was added for each intervention.	Adolescent participants will be dosed different than adult participants.
1.3 Schedule of Activities	AE collection was further clarified for ongoing drug related AEs.	Clarified per regulatory feedback.
1.3 Schedule of Activities, Appendix 2: Clinical Laboratory Tests	Urine protein was added for patients receiving cabozantinib	Monitoring added per regulatory feedback.
1.3 Schedule of Activities; 8.2 Safety Assessments	Growth plate imaging was added for patients <18 years of age who have not reached full adult height.	Monitoring added per regulatory feedback.
2.2 Background	Additional information was added for adolescent participants.	Added per regulatory feedback.
2.2.1 LOXO-292	Clarification was added on the management of hypersensitivity, liver test abnormalities, thrombocytopenia, and hypertension.	Clarified per regulatory feedback.
2.3 Benefit/Risk Assessment	Additional information on the benefit/risk for Study JZJB was added.	Added per regulatory feedback.

Section # and Name	Description of Change	Brief Rationale
4.3.2 Cabozantinib, 4.3.3 Vandetanib	Additional justification for adolescent dose was added.	Adolescent participants will be dosed different than adult participants.
5.1 Inclusion Criteria	Inclusion criteria 1 was modified to clarify patients will be permitted after giving assent/written consent.	Modified per regulatory feedback.
5.1 Inclusion Criteria	Inclusion criteria 11 was modified to clarify women of childbearing potential will be included if they are no breast feeding during treatment and at least 4 months after last study dose.	Modified per regulatory feedback.
5.2 Exclusion Criteria	Exclusion criteria 15 was updated to exclude patients with a history of Torsades de pointes.	Updated per regulatory feedback.
5.2 Exclusion Criteria	Exclusion criteria 28 was added excluding patients with a known hypersensitivity to any of the excipients of either cabozantinib or vandetanib.	Added per regulatory feedback.
6.5.3 P-gp Substrates or MRP2 Inhibitors	Section 6.5.3 was added with special instructions for patients co-administered P-gp substrates or MRP2 inhibitors.	Added per regulatory feedback.
6.6.1 Dose Modifications for LOXO-292 Hypersensitivity	Special instructions were added if hypersensitivity occurs.	Added per regulatory feedback.

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