J2G-GH-JZJK Protocol(b)

A Phase 2 Study of Oral Selpercatinib (LOXO-292) in Patients with Advanced Solid Tumors, Including *RET* Fusion-Positive Solid Tumors, Medullary Thyroid Cancer, and Other Tumors with *RET* Activation

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A Phase 2 Study of Oral Selpercatinib (LOXO-292) in Patients with Advanced Solid Tumors, Including *RET* Fusion-Positive Solid Tumors, Medullary Thyroid Cancer, and Other Tumors with *RET* Activation

Investigational Product:	Selpercatinib (LOXO-292) (LY3527723)
Protocol Number:	J2G-GH-JZJK, LIBRETTO-321
Amendment Number	b
Development Phase:	2
Sponsor:	Eli Lilly and Company Indianapolis, Indiana USA 46285
Version 1.0 (China)	Approval date below

Protocol Electronically Signed and Approved by Lilly: 30 July 2019
Amendment (a) Electronically Signed and Approved by Lilly: 20 July 2020
Amendment (b) Electronically Signed and Approved by Lilly: approval date provided below

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Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Amendment a	20-Jul-2020
Protocol J2G-GH-JZJK	30-Jul-2019

Amendment (b)

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
9.4.5 Interim Analyses and Data Monitoring	Added interim analyses section	An interim analysis is planned to assess the early efficacy of selpercatinib
Synopsis, 2.3 Exploratory Objectives, and 9.1.3 Exploratory Endpoints	An exploratory objective was added	To estimate the time from initial PD (PD_1) to subsequent PD (PD_2) to explore whether patients continue to benefit from study treatment after disease progression
6.2.3 Cycles 2 and Higher and Table 7-1 Schedule of Activity (SoA) note e	Added reconsent information for patients continuing treatment beyond PD	Clarification
Table 7-1 Schedule of Activity (SoA)	Revised screening period from 'Day -28 to Day -1' to 'Up to 28 days prior to first dose'	Clarification
Table 7-1 Schedule of Activity (SoA) and note w	Clarified disease assessment to be performed based on "week", rather than "cycle", and added post scan frequency after initial PD in note w	Clarification
Table 7-1 Schedule of Activity (SoA)	Separately displayed the visit window for intensive PK and PopPK	Clarification
Throughout the protocol	Minor formatting and editorial changes	Minor, therefore not detailed

Synopsis

TITLE:
A Phase 2 Study of Oral Selpercatinib (LOXO-292) in Patients with Advanced Solid Tumors, Including Rearranged in transfection (*RET*) Fusion-Positive Solid Tumors, Medullary Thyroid Cancer and Other Tumors with *RET* Activation

PROTOCOL NUMBER:
J2G-GH-JZJK

STUDY SITES:
Approximately 40 institutions in China are planned for participation in this study.

PHASE:
2

OBJECTIVES:

Primary Objective:

- To assess the anti-tumor activity of selpercatinib by determining objective response rate (ORR) using RECIST v1.1, as assessed by independent review committee (IRC).

Secondary Objectives:

- To assess, for each cohort, the anti-tumor activity of selpercatinib by determining:
    a. ORR based on RECIST v1.1 as assessed by Investigator;
    b. Duration of response (DOR) as assessed by IRC and Investigator;
    c. Central nervous system (CNS) ORR based on RECIST v1.1 as assessed by IRC (for patients with brain metastases);
    d. CNS DOR as assessed by IRC (for patients with brain metastases);
    e. Time to response (TTR) based on RECIST v1.1 as assessed by IRC and Investigator;
    f. Time to best response (TTBR) based on RECIST v1.1 as assessed by IRC and Investigator;
    g. Clinical benefit rate (CBR) based on the proportion of patients with best overall response of complete response (CR), partial response (PR), or stable disease (SD) lasting 16 or more weeks following initiation of selpercatinib as assessed by IRC and Investigator;
    h. Progression-free survival (PFS) as assessed by IRC and Investigator;
    i. Overall survival (OS) following initiation of selpercatinib.
- To characterize the safety profile and tolerability of selpercatinib.
- To characterize the pharmacokinetics (PK) properties of selpercatinib.

Exploratory Objectives:

- To determine the relationship between PK and drug effects, including efficacy and safety.
- To evaluate the serum tumor markers carcinoembryonic antigen (CEA) and calcitonin (for patients with MTC), thyroglobulin (for patients with non-MTC thyroid cancer, unless not measurable due to presence of anti-thyroglobulin antibodies), and adrenocorticotropic hormone (ACTH)/cortisol (for patients with Cushing's disease related to their cancer), before, during, and at the end of treatment (EOT) with selpercatinib.
- To collect patient-reported outcomes (PRO) data to explore disease-related symptoms and health-related quality of life (HRQoL).
- To estimate the time from initial progressive disease (PD_1) to subsequent PD (PD_2) to explore whether patients continue to benefit from study treatment after disease progression.

STUDY DESIGN:

This is an open label, multi-center Phase 2 study in patients with advanced solid tumors, including *RET* fusion-positive solid tumors (e.g., non-small cell lung cancer [NSCLC], thyroid, pancreas, colorectal), *RET*-mutant MTC, and other tumors with *RET* activation (e.g., mutations in other tumor types or other evidence of *RET* activation). Patients with *RET* alterations in tumor and/or blood will be identified through molecular assays. The *RET* alteration result should be generated from a laboratory with certification by China National Accreditation Service for Conformity Assessment (CNAS), External Quality Assessment (EQA), Clinical Laboratory Improvement Amendments (CLIA), College Of American Pathologists (CAP) or other similar certification. The Sponsor should be contacted to discuss test results to ensure trial eligibility.

At least 20 patients for Cohorts 1 and 2 and up to 25 patients in Cohort 3 harboring a *RET* gene alteration in tumor and/or blood (e.g., gene fusions and/or mutations, excluding synonymous, frameshift, or nonsense mutations) will be enrolled to one of three cohorts (refer to the Study Schema) as noted below. For Cohorts 1 and 2, evidence of a *RET* gene alteration in tumor (i.e., not just blood) as defined in Synopsis Table 1) is required (a positive germline test for a *RET* mutation is acceptable for patients with MTC).

Enrollment will be based on tumor type, type of *RET* alteration, and prior treatment:

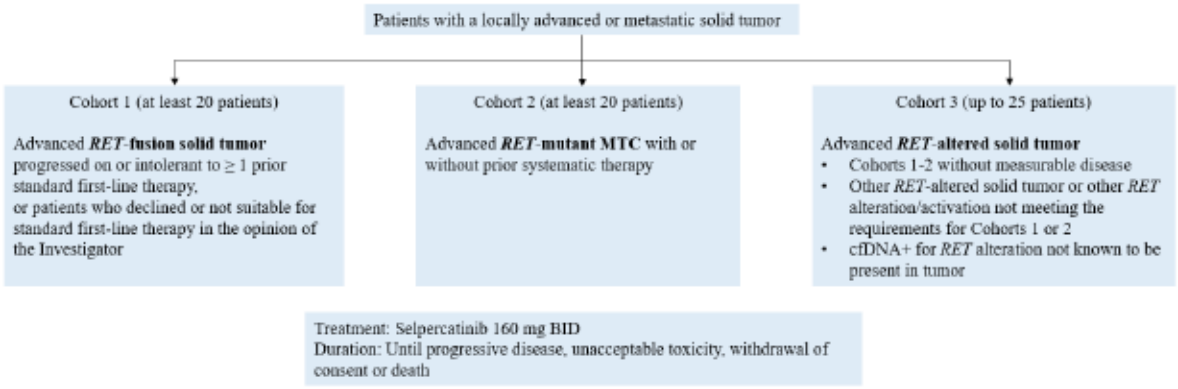
1. Cohort 1: *RET*-fusion-positive solid tumor progressed on or intolerant to ≥ 1 prior standard therapy, or patients who declined or not suitable for standard first line therapy in the opinion of the investigator. For lung cancer, only patients harboring *RET-KIF5B, RET-CCDC6, RET-NCOA4* can be enrolled in Cohort 1. For other solid tumor, patients with any *RET* fusion can be enrolled in Cohort 1 (at least 20 patients);
2. Cohort 2: *RET*-mutant MTC with or without prior systematic therapy (at least 20 patients);
3. Cohort 3 (up to 25 patients):
   - Cohorts 1-2 without measurable disease;
   - Other *RET*-altered solid tumor or other *RET* alteration/activation not meeting the requirements for Cohorts 1 or 2;MTC syndrome spectrum cancers (e.g. MTC, pheochromocytoma) with neuroendocrine features/differentiation or poorly differentiated thyroid cancers with other RET alteration/activation may be allowed with prior sponsor approval;
   - Known cfDNA positive for a *RET* gene alteration not known to be present in a tumor sample may be allowed with sponsor approval;
   - Fluorescence in situ hybridization (FISH) positive in tumor without polymerase chain reaction (PCR)/ next generation sequencing (NGS) result may be allowed with sponsor's approval.

Synopsis Table 1: Definition of *RET* Alterations

RET* mutation
Previously reported activating *RET* gene mutation, excluding synonymous, frameshift or nonsense mutations. Refer to Appendix B for examples. For MTC, *RET* gene mutation not known to be activating may be enrolled with sponsor's approval, to Cohort 3.
RET* fusion
By PCR or NGS (FISH as the only molecular result is acceptable for Cohort 3, but not Cohort 1).
RET* mutation or *RET* fusion
No other known validated driver alteration(s). Refer to Appendix C for examples.
* According to laboratory with CNAS, EQA, CLIA, CAP or similar certification, so long as a written Molecular Pathology Report is available and clearly asserts the presence of the referenced *RET* alteration.

Abbreviations: FISH-Fluorescence In Situ Hybridization; MTC-Medullary Thyroid Cancer; NGS-Next Generation Sequencing; PCR-Polymerase Chain Reaction.

Study Schema



Primary endpoint: ORR per RECIST v1.1 by independent review committee

Secondary endpoint: ORR per RECIST v1.1 by investigator, DOR, CNS ORR, CNS DOR, CBR, TTR, TTBR, PFS, OS, PK, safety

Abbreviations: BID-twice daily; MTC-medullary thyroid cancer; cfDNA-circulating free tumor deoxyribonucleic acid. DOR- duration of response, CNS ORR- central nervous system objective response rate, CNS DOR- central nervous system duration of response, CBR- clinical benefit rate, TTR- time to response, TTBR- time to best response, PFS-progression-free survival, OS- overall survival, PK- pharmacokinetic

ELIGIBILITY CRITERIA:

Inclusion Criteria:

1. Patients with a locally advanced or metastatic solid tumor who:
   - have progressed on or are intolerant to standard therapy, or
   - no standard therapy exists, or in the opinion of the Investigator, are not candidates for or would be unlikely to tolerate or derive significant clinical benefit from standard therapy, or
   - decline standard therapy.
2. Prior MKIs with anti-RET activity are allowed. Refer to Appendix A for examples of MKIs with anti-RET activity. However, prior treatment with a selective RET inhibitor(s) (including investigational selective RET inhibitor(s), such as BLU-667, RXDX-105) is prohibited. The specific agent(s), duration of treatment, clinical benefit, and reason for discontinuation (e.g., PD, drug toxicity, or intolerance) should be documented for all kinase inhibitors the patient has been exposed to.
3. Evidence of a *RET* gene alteration in tumor and/or blood (e.g., gene rearrangement and/or mutation, excluding synonymous, frameshift, or nonsense mutations), as identified through molecular assays, as performed for clinical evaluation. The *RET* alteration result should be generated from a laboratory with certification by CNAS, EQA, CLIA, CAP or other similar certification. The Sponsor should be contacted to discuss test results from labs where such certification is not clearly demonstrated to determine eligibility.
4. Measurable or non-measurable disease as determined by RECIST v1.1.
5. At least 18 years of age.
6. Eastern Cooperative Oncology Group (ECOG) performance status score of 0, 1, or 2, with no sudden deterioration 2 weeks prior to the first dose of study treatment.
7. Life expectancy of at least 3 months.
8. Archived tumor tissue sample available for Cohort 1 and 2.
9. Adequate hematologic status, defined as:
   - Absolute neutrophil count (ANC) $\geq 1.0 \times 10^9$/L not requiring growth factor support for at least 7 days prior to treatment, and
   - Platelet count $\geq 75 \times 10^9$/L not requiring transfusion support for at least 7 days prior to treatment, and

- Hemoglobin (Hb) ≥ 9 g/dL not requiring transfusion support or erythropoietin for at least 7 days prior to treatment.

10. Adequate hepatic function, defined as:
    - Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≤ 2.5 × the upper limit of normal (ULN) or ≤ 5 × ULN with documented liver involvement (such as liver metastasis or a primary biliary tumor) and
    - Total bilirubin ≤ 1.5 × ULN or ≤ 3 × ULN with documented liver involvement (patients with Gilbert's Disease may be enrolled with prior Sponsor approval).
11. Adequate renal function, with estimated glomerular filtration rate (eGFR) ≥ 30 mL/minute. Sites can use their own clinical standard for eGFR. If no clinical standard, below Modification of Diet in Renal Disease (MDRD) study equation can be used: eGFR (mL/min/1.73 m^2) = 175 × $(S_{cr}/88.4)^{-1.154}$ × $(Age)^{-0.203}$ × (0.742 if female) × (1.212 if African American) (SI units). <<
12. Ability to swallow capsules and comply with outpatient treatment, laboratory monitoring, and required clinic visits for the duration of study participation.
13. Willingness of men and women of reproductive potential to observe conventional and effective birth control for the duration of treatment and for 3 months following the last dose of study treatment; this may include barrier methods such as a condom or diaphragm with spermicidal gel. Male study participants should refrain from sperm donation during study treatment and up to 6 months following the last dose of selpercatinib.
14. Written informed consent and any local required authorization (e.g., Health Insurance Portability and Accountability Act in the US, European Union [EU] Data Privacy Directive in the EU) obtained from the patient/legal representative prior to performing any protocol-related procedures, including screening evaluations.
15. Cohorts 1 and 2: failed or intolerant to standard of care; see Synopsis Table 2 for Examples.

Synopsis Table 2: Standard of Care Therapies for Cohort 1 and 2

COHORT	THERAPY
Cohort 1: *RET* Fusion-Positive Solid Tumor	NSCLC: platinum-based chemotherapy (or other chemotherapy if not eligible for platinum) or PD-1/PD-L1 immunotherapy or both Thyroid: sorafenib, patients must also be radioactive iodine-refractory as appropriate Colorectal: fluoropyrimidine-based chemotherapy, with or without anti-VEGF-directed therapy or anti-EGFR-directed therapy as appropriate for the disease Pancreas: fluoropyrimidine-based, gemcitabine-based, or S-1 chemotherapy Breast: anthracycline, taxane, HER2-directed therapy and/or hormonal therapy or other standard therapy appropriate for the disease Other: prior standard therapy for the disease
Cohort 2: *RET*-mutant MTC	No approved SOC

Abbreviations: EGFR-epidermal growth factor receptor; HER2-human epidermal growth factor receptor 2; MTC-medullary thyroid cancer; NSCLC-non-small cell lung cancer; PD-1-programmed cell death protein 1; PD-L1-programmed death-ligand 1; VEGF-vascular endothelial growth factor.

16. Cohorts 1-2: enrollment will be restricted to patients with evidence of a *RET* gene alteration in tumor (i.e., not just blood) as defined in Synopsis Table 1. However, a positive germline DNA test for a *RET* gene mutation as defined in Appendix B (Table 11-2) is acceptable in the absence of tumor tissue testing for patients with MTC.
17. Cohorts 1-2: at least one measurable lesion as defined by RECIST v1.1 and not previously irradiated (unless PD for the irradiated lesion[s] has been radiographically documented).
18. Cohort 2: radiographic PD within the previous 14 months for systematic treatment naïve patient.

Exclusion Criteria:

19. Cohorts 1-2, an additional validated oncogenic driver that could cause resistance to selpercatinib treatment if known. See Appendix C (Table 11-3) for examples.
20. Prior treatment with a selective RET inhibitor(s) (including investigational selective RET inhibitor(s), such as BLU-667, RXDX-105, etc.).
21. Are currently enrolled in any other clinical study involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study.
22. Investigational agent or anticancer therapy within 5 half-lives or 2 weeks (whichever is shorter) prior to planned start of selpercatinib. In addition, no concurrent investigational anti-cancer therapy is permitted.
23. Major surgery (excluding placement of vascular access or biopsy) within 4 weeks prior to planned start of selpercatinib.
24. Radiotherapy with a limited field of radiation for palliation within 1 week of the first dose of study treatment, with the exception of patients receiving radiation to more than 30% of the bone marrow or with a wide field of radiation, which must be completed at least 4 weeks prior to the first dose of study treatment.
25. Any unresolved toxicities from prior therapy greater than CTCAE Grade 1 except where otherwise noted in this eligibility criteria at the time of starting study treatment with the exception of alopecia and Grade 2, prior platinum therapy-related neuropathy.
26. Symptomatic primary CNS tumor, symptomatic CNS metastases, leptomeningeal carcinomatosis, or untreated spinal cord compression.

    Exception: Patients are eligible if neurological symptoms and CNS imaging are stable and steroid dose is stable for 14 days prior to the first dose of selpercatinib and no CNS surgery or radiation has been performed for 28 days, 14 days if stereotactic radiosurgery [SRS].

    Note: All prior local treatments for CNS disease (e.g. surgery, whole brain radiation [WBRT], SRS), the start and stop dates for each prior local therapy, the specific lesions treated (if SRS and/or surgery), whether the patient developed intracranial progression after the last prior local treatment, and which lesions progressed since completion of the local therapy must be documented.
27. Clinically significant active cardiovascular disease or history of myocardial infarction within 6 months prior to planned start of selpercatinib or prolongation of the QT interval corrected for heart rate using Fridericia's formula (QTcF) > 470 msec. Correction of suspected drug-induced QTcF prolongation may be attempted at the investigator's discretion if clinically safe to do so.
28. History of Human Immunodeficiency Virus (known HIV 1/2 antibodies positive); patients with unknown HIV status do not need to be tested.
29. History of active hepatitis B (known positive hepatitis B surface antigen [HbsAg] and quantitative hepatitis B DNA greater than the upper limit of detection of the assay) or C (known positive hepatitis C antibody and quantitative hepatitis C RNA greater than the upper limit of detection of the assay); patients with unknown hepatitis B/hepatitis C status do not need to be tested.
30. Active uncontrolled systemic bacterial, viral, or fungal infection or serious ongoing intercurrent illness, such as hypertension or diabetes, despite optimal treatment. Screening for chronic conditions is not required.
31. Clinically significant active malabsorption syndrome or other condition likely to affect gastrointestinal absorption of the study drug.
32. Uncontrolled symptomatic hyperthyroidism or hypothyroidism.
33. Uncontrolled symptomatic hypercalcemia or hypocalcemia.
34. Concurrent use of drugs known to prolong QTc (refer to Appendix D of the main protocol)
35. Pregnancy or lactation. Breast-feeding should be interrupted when selpercatinib is started; breast-feeding can be resumed 3 months after discontinuation of selpercatinib.
36. Active second malignancy other than minor treatment of indolent cancers with prior sponsor approval.

PLANNED SAMPLE SIZE:

The study will enroll approximately 75 patients in total.

INVESTIGATIONAL PRODUCT:

Selpercatinib will be provided in a capsule in 40 mg and 80 mg dose strengths. The capsules will be provided to the sites for distribution to the patient for outpatient administration at the assigned dose level. Dosing is intended to be fixed (i.e., not weight-based or body surface area [BSA]-based).

TREATMENT PROCEDURES:

Patients will begin dosing on Cycle 1 Day 1 (C1D1) according to the assigned cohort with cycle length of 28 days. Individual patients will continue selpercatinib dosing until PD, unacceptable toxicity, or other reason for treatment discontinuation. Patients with documented PD may be allowed to continue selpercatinib if the patient is tolerating treatment and, in the opinion of the Investigator, the patient is deriving clinical benefit from continuing study treatment and continuation of treatment is approved by the Sponsor.

STUDY ASSESSMENTS:

Safety observations include physical examinations, body weight, ECOG score, clinical AEs, laboratory variables (hematology, serum chemistries, and urinalysis), electrocardiogram (ECG), vital signs, and thyroid function.

Efficacy assessments include tumor evaluation every 8 weeks beginning with Cycle 3 Day 1 (C3D1) (±7 days) through C13D1, and approximately every 12 weeks thereafter. In addition, Investigators may conduct an initial tumor evaluation on C2D1 (±7 days) and a confirmatory tumor evaluation a minimum of 4 weeks (i.e., 28 days) after the first tumor evaluation that shows a CR or PR by RECIST v1.1, if consistent with local regulatory authority requirements. In fusion-positive solid tumors, patients with a history of CNS metastases, brain metastases at baseline, or other clinically syndrome required brain imaging, the baseline and subsequent serial scans will be performed. All scans will be collected and stored at a central facility to permit central reviewer assessment, for the purpose of confirming PD if not occurring on study, subsequent anticancer therapy(ies), and survival. Long-term follow-up (LTFU) may be conducted by phone. For any patient who is lost to follow-up, the study site will attempt to ascertain survival information via public database search. If survival status still cannot be ascertained, patients will be considered lost to follow-up and will be censored appropriately. Patients who discontinue study treatment for reasons other than PD, withdrawal of consent or initiation of a new anticancer therapy(ies), may (but for practical reasons and to minimize patient inconvenience, are not required to) undergo disease assessment by imaging (as specified above) until PD, withdrawal of consent or initiation of a new anticancer therapy(ies).

Serial blood samples for intensive PK monitoring will be collected on C1D1 and C1D8 for a total of 12 patients, blood samples for population pharmacokinetic (PopPK) will be collected for all enrolled patients.

Archived tumor tissue will be obtained for patients if available and stored by the Sponsor. Patients who do not have adequate archival tumor tissue available should undergo a fresh tumor biopsy, if it is considered safe to perform, prior to treatment. If archived tumor tissue is not available and a fresh biopsy cannot be safely performed, the patient may still be eligible with prior Sponsor approval. Additionally, optional fresh tumor biopsies should be obtained prior to treatment with selpercatinib if archived tumor tissue was obtained prior to progression on the last MKI with anti-RET activity and at progression.

HRQoL instruments (European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 [EORTC QLQ-C30] will be administered pre-dose on C1D1 and subsequent assessments will occur at the same cycle visits as disease assessments until EOT. For MTC patients with diarrhea present at baseline, bowel assessments will be collected pre-dose C1D1, weekly for the first cycle, and at D1 of each cycle until EOT.

STUDY ENDPOINTS:

Primary Endpoint:

- ORR based on RECIST v1.1 assessed by IRC.

Secondary Endpoints:

- Parameters of anti-tumor activity/clinical benefit, including: ORR (by Investigator), DOR (by IRC and Investigator), CNS ORR (by IRC), CNS DOR (by IRC), TTR (time to response), TTBR (time to best response by IRC and Investigator), CBR (by IRC and Investigator), PFS (by IRC and Investigator), and OS.
- Frequency, severity, and relatedness of treatment-emergent adverse events (TEAEs) and Serious Adverse Events (SAEs), changes in hematology and blood chemistry values, assessments of physical examinations, vital signs, and ECGs.

- Plasma concentrations of selpercatinib and PK parameters, including, but not limited to, AUC_{0-24}, C_{max}, and T_{max}.

Exploratory Endpoints:

- Differences in efficacy and safety based on selpercatinib PK parameters.
- Changes in CEA and calcitonin (for patients with MTC), thyroglobulin (non-MTC patients), ACTH and cortisol (patients with Cushing's disease related to their cancer) with selpercatinib treatment.
- Changes from baseline in disease-related symptoms and HRQoL, as measured by EORTC QLQ-C30 (adults), and patient bowel diaries (MTC patients only).
- Time from PD_1 to PD_2 for patients who continue to receive study treatment beyond disease progression.

STATISTICAL METHODS:

Safety Analyses:

The safety population will consist of all enrolled patients who receive at least one dose of selpercatinib.
A baseline measurement and at least one laboratory or other safety-related measurement obtained after treatment of study drug may be required for inclusion in the analysis of a specific safety parameter.

Efficacy Analyses:

The efficacy analysis will be conducted on all treated patients enrolled in Cohort 1 and 2 who have confirmed *RET* fusion positive solid tumor or *RET* mutant MTC by central lab, respectively.

ORR will be estimated based on the observed proportion of patients whose best overall response is confirmed CR or PR as determined by IRC and by the treating Investigator. The estimates of the ORR will be accompanied by a 2-sided 95% exact binomial confidence interval (CI). Waterfall plots will be used to depict graphically the maximum decrease from baseline in the sum of diameters of target lesions. The duration of response, PFS, and OS will be summarized descriptively for each cohort using the Kaplan-Meier method.

Pharmacokinetic Analyses:

Plasma concentrations of selpercatinib will be determined with a validated bioanalytical assay. The following PK parameters will be calculated from plasma concentrations determined on Cycle 1 Day 1 and Day 8: C_{max}, T_{max}, area under the concentration versus time curve from time 0 to t (AUC_{0-t}), area under the concentration time curve from time 0 to infinity ($AUC_{0-\infty}$), apparent oral clearance (CL/F), apparent volume of distribution (Vz/F), and terminal elimination half-life ($T_{1/2}$). Summary statistics will be generated by cohort as appropriate.

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List of Abbreviations and Definition of Terms

Abbreviation or Term	Definition
AE	adverse event
ACTH	adrenocorticotropic hormone
ALK	anaplastic lymphoma kinase
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
anti-PD1	anti-programmed cell death protein 1
AST	aspartate aminotransferase
ATP	adenosine triphosphate
AUC	area under the concentration vs time curve
$AUC_{0-\infty}$	area under the concentration versus time curve from time 0 extrapolated to infinity
AUC_{0-t}	area under the concentration versus time curve from time 0 to t
AUC_{0-24}	area under the concentration versus time curve from time 0 to 24 hours
AUC_{tau}	area under the concentration versus time curve calculated during the dosing interval at steady state
BID	twice daily
BUN	blood urea nitrogen
BSA	body surface area
C	Cycle
C1D1	Cycle 1 Day 1
CAP	College of American Pathologists
CBR	clinical benefit rate
CDMS	Clinical Data Management System
CEA	carcinoembryonic antigen
cfDNA	circulating free deoxyribonucleic acid
CI	confidence interval
CL/F	apparent oral clearance of drug
C_{max}	maximum drug concentration
C_{min}	minimum drug concentration
CNAS	China National Accreditation Service for Conformity Assessment
CNS	central nervous system
CR	complete response
CT	computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events

Abbreviation or Term	Definition
CYP	cytochrome P450
D	Day
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
EGFR	epidermal growth factor receptor
EORTC	European Organization for Research and Treatment of Cancer
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
EOT	end of treatment
ER	estrogen receptor
FAS	Full Analysis Set
FGFR	fibroblast growth factor receptor
FISH	Fluorescence in Situ Hybridization
FLAIR/T2	T2-weighted fluid-attenuated inversion recovery
GALT	gastrointestinal associated lymphoid tissues
GCP	Good Clinical Practices
GI	gastrointestinal
GLP	Good Laboratory Practice
GnRH	gonadotropin-releasing hormone
5-HT3	serotonin type 3
H2	histamine-2
Hb	Hemoglobin
hERG	Human ether-à-go-go related gene
HRQoL	Health-Related Quality of Life
IB	Investigator's Brochure
IC_{50}	50% inhibitory concentration
ICF	informed consent form
ICH	International Conference on Harmonisation
ICH GCP	International Conference on Harmonisation-Good Clinical Practices

Abbreviation or Term	Definition
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRC	independent review committee
ISO/IEC	International Organization for Standardization/ Independent Ethics Committee
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	Intravenous
KRAS	Kirsten rat sarcoma virus oncogene
LDH	lactate dehydrogenase
LFTs	liver function tests
LHRH	luteinizing hormone-releasing hormone
LOXO-292	investigational product (selpercatinib)
LTFU	Long-term Follow-up
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
MHC-I	Major Histocompatibility Complex class I
MKIs	multikinase inhibitors
MRI	magnetic resonance imaging
MTC	medullary thyroid cancer
NCI	National Cancer Institute
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NGS	next-generation sequencing
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
PCR	polymerase chain reaction
PD	progressive disease
PD_1	initial progressive disease
PD_2	subsequent progressive disease
PD-1	programmed cell death protein 1
PD-L1	programmed death-ligand 1
PedsQL	Pediatric Quality of Life Inventory-Core Module
PET	positron emission tomography
PFS	progression-free survival
P-gp	p-glycoprotein
PK	pharmacokinetic

Abbreviation or Term	Definition
PO	per os (oral)
PopPK	population pharmacokinetic
PP	Per-protocol Analysis Set
PPI	proton pump inhibitors
PR	partial response
PRO	patient-reported outcomes
PTC	papillary thyroid cancer
QD	once daily
QTcF	QT interval corrected for heart rate (Fridericia's formula)
QTcI	individual animal heart rate corrected QT intervals
RBC	red blood cell(s)
REB	Research Ethics Board
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended Phase 2 dose
RTK	receptor tyrosine kinase
SAD	short axis diameter
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SERDs	selective estrogen receptor degraders
SERMs	selective estrogen receptor modulators
SFU	safety follow-up
SOC	system organ class
SOD	sum of the diameters
SRC	Safety Review Committee
SRS	stereotactic radiosurgery
SUSARs	suspected unexpected serious adverse reactions
$T_{1/2}$	terminal elimination half-life
FT_3	Free triiodothyronine
FT_4	Free thyroxine
TBD	to be determined
TBL	total bilirubin level
TEAE	treatment-emergent adverse event
TKIs	tyrosine kinase inhibitors
T_{max}	time to maximum plasma concentration
TSH	thyroid stimulating hormone

Abbreviation or Term	**Definition**
ULN	upper limit of normal
US	United States
V_z/F	apparent volume of distribution
WBC	white blood cell
WBRT	whole brain radiation therapy

1 Introduction

1.1 Tumors with RET Abnormalities and Current Treatment Options

Rearranged in transfection (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 two 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, Ritz 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 ~6% of sporadic papillary thyroid cancers (PTCs) (Fusco, Grieco et al. 1987, Cancer Genome Atlas Research 2014) and at even higher frequency in radiation-induced PTCs (Ito, Seyama et al. 1994, Fugazzola, Pilotti et al. 1995, Bounacer, Wicker et al. 1997, Nikiforov, Rowland et al. 1997). In patients with PTC, *RET* gene fusions are associated with adverse prognostic features (Prasad, Vyas et al. 2016, Su, He et al. 2016). In addition, activating *RET* gene mutations occur at high frequency in human medullary thyroid cancer (MTC) (>90% hereditary, ~50–60% sporadic) (Donis-Keller, Dou et al. 1993, Mulligan, Kwok et al. 1993, Carlson, Dou et al. 1994, Eng, Smith et al. 1994, Hofstra, Landsvater et al. 1994, Agrawal, Jiao et al. 2013, Ji, Oh et al. 2015). The application of NGS approaches to a large collection of human tumors has led to the identification of *RET* gene fusions in a small fraction (1 to 2%) of non-small cell lung cancers (NSCLC; adenocarcinomas) and in an even smaller fraction of other tumor types, including colorectal cancer, breast cancer and chronic myeloproliferative neoplasms (Ballerini, Struski et al. 2012, Ju, Lee et al. 2012, Kohno, Ichikawa et al. 2012, Lipson, Capelletti et al. 2012, Takeuchi, Soda et al. 2012, Bossi, Carlomagno et al. 2014, Stransky, Cerami et al. 2014).

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, Breuleux et al. 2008, Wang, Mayer et al. 2012), a finding that is consistent with 1) possible ER-mediated increased RET expression in tumors from rare families with MTC (Smith, Read et al. 2016); 2) increased RET expression in some ER-positive breast cancers that have acquired resistance to anti-estrogens (Plaza-Menacho, Morandi et al. 2010, Spanheimer, Park et al. 2014); and 3) re-sensitization to anti-estrogen treatment through RET inhibition (Plaza-Menacho, Morandi et al. 2010, Morandi, Martin et al. 2013, Spanheimer, Park 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, Oh et al. 2016). This finding suggests a possible role for RET inhibition in upregulating the anti-cancer immune response.

The combination of low-frequency alterations in a highly prevalent cancer like NSCLC, high-frequency alterations in a less-prevalent cancer like MTC and potential additional roles for RET in other contexts indicates that a significant number of patients with advanced, *RET*-fusion NSCLC, *RET*-mutant MTC, and other cancers with *RET* activation could benefit from potent and selective RET kinase inhibition.

Several multikinase inhibitors (MKIs) with some degree of anti-RET activity are already in the clinic and 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, Robinson et al. 2012, Elisei, Schlumberger et al. 2013). 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, Robinson et al. 2012, Sherman, Clary 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%-53% (depending on the specific MKI

and patient population), but PFS times of only 3.6 to 7.3 months, in several ongoing Phase 2 studies (Drilon, Rekhtman et al. 2016, Lee 2016, Velcheti 2016, Yoh, Seto et al. 2016).

The efficacy of these MKIs is ultimately limited by incomplete inhibition of RET in tumors, significant toxicity from stronger inhibition of other targets (e.g., KDR/VEGFR2, EGFR, MET), and poor pharmacokinetics (PK) (i.e., significant drug accumulation and long half-life contributing to toxicity, but not efficacy) in patients. As a result, the majority of patients treated with these agents experience significant toxicities requiring dose interruptions, reductions, and/or treatment cessation.

Patients with *RET*-fusion-positive cancers (NSCLC, PTC, colon, others) and *RET*-mutant cancers (such as MTC) represent populations with high unmet need. Combination chemotherapy has short-term palliative potential in advanced NSCLC(Borghaei, Paz-Ares et al. 2015, Rizvi, Hellmann et al. 2015, Gainor, Shaw et al. 2016, Herbst, Baas et al. 2016). Chemotherapy is ineffective for MTC and PTC. 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.

1.2 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 tumors (such as NSCLC, MTC, PTC, and colon or breast carcinomas) that harbor *RET* alterations and/or depend on RET activation. This Phase 2 study of selpercatinib is required to understand the preliminary assessment of efficacy for selpercatinib in Chinese patients and further determine the safety profile and PK properties of selpercatinib.

1.3 Selpercatinib Pre-clinical Data Summary

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 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 five 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.

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

1.4 Determination Starting Dose

The dose of 160 mg twice daily (BID) was selected as the recommended Phase 2 dose (RP2D) based on the safety data (N=82) and preliminary efficacy data in 64 evaluable patients treated at doses from 20 mg once daily (QD) through 240 mg BID (Drilon 2018). Additional information is provided in the selpercatinib IB.

1.5 Clinical Experience

As of a data cutoff of December 16, 2019, efficacy of selpercatinib was evaluated in patients with *RET* fusion-positive NSCLC, *RET*-mutant MTC, and *RET* fusion-positive thyroid cancer treated on LIBRETTO-001.

Efficacy was evaluated in 105 patients with *RET* fusion-positive NSCLC previously treated with platinum chemotherapy. In these patients, the objective response rate (ORR) was 64% (95% CI 54, 73) by Independent Review Committee (IRC) assessment. The median duration of response

(DOR) by IRC was 17.5 months (95% CI: 12.0, not estimable [NE]). In 39 patients with treatment-naive *RET* fusion-positive NSCLC, the ORR was 85% (95% CI: 70, 94) by IRC assessment. The median DOR by IRC was not reached (95% CI: 12.0, NE).

Efficacy was evaluated in 55 patients with *RET*-mutant MTC previously treated with cabozantinib or vandetanib. In these patients, the ORR was 69% (95% CI: 55, 81) by IRC assessment. The median DOR by IRC assessment was not reached (95% CI: 19.1, NE). In 88 patients with *RET*-mutant MTC who were cabozantinib and vandetanib treatment-naïve, the ORR was 73% (95% CI: 62, 82) by IRC assessment. The median DOR by IRC assessment was 22.0 months (95% CI: NE, NE). In 19 patients with previously treated *RET* fusion-positive thyroid cancer, the ORR was 79% (95% CI: 54, 94) by IRC. The median DOR by IRC was 18.4 months (95% CI: 7.6, NE).

As of March 30, 2020, a total of 734 of the 744 patients (98.7%) treated in LIBRETTO-001 experienced at least 1 TEAE (regardless of relationship to study drug) of any grade. The TEAEs were coded according to the Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC). Across 9 dose levels ranging from 20 mg QD to 240 mg BID in these 744 patients, TEAEs occurring in ≥ 15% patients were: dry mouth (39.7% total; 35.2% related), diarrhea (38.2% total; 21.8% related), hypertension (36.3% total; 25.1% related), AST increased (31.9% total; 25.9% related), ALT increased (31.5% total; 25.9% related), fatigue (30.8% total; 19.2% related), constipation (26.6% total; 12.8% related), edema peripheral (25.3% total; 14.1% related), nausea (23.3% total; 10.1% related), headache (23.3% total; 8.6% related), blood creatinine increased (20.2% total; 11.6% related), abdominal pain (19.5% total; 5.9% related), rash (18.1% total; 11.3% related), electrocardiogram QT prolonged (17.5% total; 13.6% related), cough (15.9% total; 1.1% related), vomiting (15.9% total; 4.3% related), and dyspnea (15.2% total; 1.6% related).

A total of 441 (59.3%) patients across all dose levels in LIBRETTO-001 had Grade 3-4 TEAEs. Grade 3-4 TEAEs that were considered to be related to study drug were reported in 239 (32.1%) patients across all dose levels. TEAEs included hypertension (19.0%; 12.1% related), ALT increased (9.8%; 8.1% related), AST increased (7.8%; 6.0% related), hyponatremia (5.8%; 0.4% related), ECG QT prolonged (4.0%; 2.8% related), lymphopenia (4.0%; 1.1% related), diarrhea (3.5%; 1.6% related), thrombocytopenia (2.8%; 2.0% related), and pneumonia (2.8%; none

related), dyspnea (2.6%; none related), neutropenia (2.4%; 1.5% related), anemia and hypocalcemia (each 2.2%, each 0.4% related), and hypophosphatemia (2.2%, 0.1% related). All other Grade 3-4 TEAEs occurred in less than 2% of patients overall. Overall, 32 (4.3%) patients have died within 28 days of the last dose of study drug, and no deaths have been attributed to study drug.

Additional details are provided in the selpercatinib IB.

1.6 Benefit and Risk Assessment

When viewed as a whole, the preclinical data indicate that selpercatinib is a highly potent and specific inhibitor of the RET RTK, with minimal inhibition of other kinase and non-kinase off targets. Since selpercatinib is an experimental medicine, it is possible that unforeseen, unknown, or unanticipated drug reactions and toxicities may occur. However, as detailed below, this clinical protocol is designed to mitigate risks to patients through a detailed plan for careful safety monitoring, systematic review of adverse events (AEs), serious AEs (SAEs), and PK, and active pharmacovigilance review to assess for safety signals or trends.

Patients with *RET*-fusion-positive cancers (NSCLC, PTC, colon, others) and *RET*-mutant MTC represent populations with high unmet need. As discussed in Section 1.1, available therapies for these patients provide short-term palliation (i.e., chemotherapy) that may be less effective in cancers driven by kinase fusions (i.e., immunotherapy) and/or are very toxic (i.e., MKIs). 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.

These considerations support evaluation of selpercatinib in the proposed patient population.

More information about the known and expected benefits, risks, SAEs and reasonably anticipated AEs of selpercatinib are to be found in the IB.

1.6.1 Known and Anticipated Risks

As of a clinical data cut-off (March 30, 2020) for the LIBRETTO-001 first-in-human (FIH) dose finding study, the following TEAEs occurred in ≥ 15% of patients (regardless of attribution to study drug):

- Dry mouth (39.7% total; 35.2% related)
- Diarrhea (38.2% total; 21.8% related)
- Hypertension (36.3% total; 25.1% related)
- AST increased (31.9% total; 25.9% related)
- ALT increased (31.5% total; 25.9% related)
- Fatigue (30.8% total; 19.2% related)
- Constipation (26.6% total; 12.8% related)
- Edema peripheral (25.3% total; 14.1% related)
- Nausea (23.3% total; 10.1% related)
- Headache (23.3% total; 8.6% related)
- Blood creatinine increased (20.2% total; 11.6% related)
- Abdominal pain (19.5% total; 5.9% related)
- Rash (18.1% total; 11.3% related)
- Electrocardiogram QT prolonged (17.5% total; 13.6% related)
- Cough (15.9% total; 1.1% related)
- Vomiting (15.9% total; 4.3% related)
- Dyspnea (15.2% total; 1.6% related)

Additional details are provided in the selpercatinib IB.

1.6.2 Potential Drug Interactions

Selpercatinib has pH-dependent solubility and its PK can be affected by agents that modify gastric pH, such as proton pump inhibitors (PPIs) (e.g., omeprazole). Coadministration with multiple daily doses of omeprazole (PPI) decreased selpercatinib $AUC_{0\text{-}INF}$ and C_{max} by 69% and 88%, respectively when selpercatinib was administered fasting. Coadministration with multiple daily doses of omeprazole did not significantly change the selpercatinib $AUC_{0\text{-}INF}$ and C_{max} when selpercatinib was administered with food.

No clinically significant differences in selpercatinib PK were observed when coadministered with multiple daily doses of ranitidine (H2 receptor antagonist) given 10 hours prior to and 2 hours after the selpercatinib dose (administered fasting). The effect of antacids that contain aluminum,

magnesium, calcium, simethicone, or buffered medicines on the PK of selpercatinib has not been specifically studied.

Coadministration of multiple doses of itraconazole (strong CYP3A inhibitor) increased the selpercatinib $AUC_{0\text{-}INF}$ by 133% and C_{max} by 30%; coadministration of multiple doses of diltiazem, fluconazole, or verapamil (moderate CYP3A inhibitors) is predicted to increase the selpercatinib AUC by 60 to 99% and C_{max} by 46 to 76%; coadministration of multiple doses of rifampin (strong CYP3A inducer) decreased the selpercatinib $AUC_{0\text{-}INF}$ by 87% and C_{max} by 70%; coadministration of multiple doses of bosentan or efavirenz (moderate CYP3A inducers) is predicted to decrease the selpercatinib AUC by 40 to 70% and C_{max} by 34 to 57%; coadministration of multiple doses of modafinil (weak CYP3A inducer) is predicted to decrease the selpercatinib AUC by 33% and C_{max} by 26%. Therefore, coadministration of selpercatinib with strong and moderate CYP3A inhibitors, strong and moderate CYP3A inducers, and CYP2C8 and CYP3A substrates should be avoided.

Coadministration of selpercatinib with repaglinide (sensitive CYP2C8 substrate) increased the repaglinide $AUC_{0\text{-}INF}$ by 188% and C_{max} by 91%. Avoid coadministration of selpercatinib with sensitive CYP2C8 substrates.

Coadministration of selpercatinib with midazolam (sensitive CYP3A) increased the midazolam $AUC_{0\text{-}INF}$ by 54% and C_{max} by 39%. Therefore, selpercatinib can be considered a weak inhibitor of CYP3A4. Coadministration of selpercatinib with sensitive CYP3A4 substrates may increase their plasma concentrations, which may increase the incidence or severity of adverse reactions. Avoid coadministration of selpercatinib with sensitive CYP3A4 substrates.

Selpercatinib does not inhibit or induce CYP1A2, CYP2B6, CYP2C9, CYP2C19, or CYP2D6 at clinically relevant concentrations.

Selpercatinib inhibits MATE1, P-gp, and BCRP, but does not inhibit OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, BSEP, and MATE2-K at clinically relevant concentrations. Selpercatinib may increase serum creatinine by decreasing renal tubular secretion of creatinine via inhibition of MATE1. Selpercatinib is a substrate for P-gp and BCRP, but not for OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, MATE1, or MATE2-K. Selpercatinib may increase serum creatinine by decreasing renal tubular secretion of creatinine via inhibition of MATE1. Consider alternative markers of renal function if persistent elevations in serum creatinine are observed. The potential

for selpercatinib inhibition of P-gp or BCRP in the intestine cannot be ruled out. If coadministration of a sensitive P-gp or BCRP substrate cannot be avoided, patients should be monitored for increased adverse reactions of these drugs.

Additional details are provided in the selpercatinib IB.

2 Study Objectives

2.1 Primary Objective

- To assess the anti-tumor activity of selpercatinib by determining ORR using RECIST v1.1 as assessed by IRC.

2.2 Secondary Objectives

- To assess the anti-tumor activity of selpercatinib by determining
  - ORR based on RECIST v1.1 as assessed by Investigator;
  - Duration of response (DOR) as assessed by IRC and Investigator;
  - Central nervous system (CNS) ORR based on RECIST v1.1 as appropriate to tumor type, as assessed by IRC (for patients with brain metastases);
  - CNS DOR as assessed by IRC (for patients with brain metastases);
  - Time to response (TTR) based on RECIST v1.1 as appropriate to tumor type, as assessed by IRC and Investigator;
  - Time to best response (TTBR) based on RECIST v1.1 as appropriate to tumor type, as assessed by IRC and Investigator;
  - Clinical Benefit Rate (CBR) based on the proportion of patients with best overall response of complete response (CR), partial response (PR), or stable disease (SD) lasting 16 or more weeks following initiation of selpercatinib, as assessed by IRC and Investigator;
  - Progression-free survival (PFS) as assessed by IRC and Investigator;
  - Overall survival (OS) following initiation of selpercatinib.
- To determine the safety profile and tolerability of selpercatinib.
- To characterize the PK properties of selpercatinib.

2.3 Exploratory Objectives

- To determine the relationship between PK and drug effects, including efficacy and safety.
- To evaluate the serum tumor markers, carcinoembryonic antigen (CEA) and calcitonin (for patients with MTC), thyroglobulin (for patients with non-MTC thyroid cancer, unless not measurable due to presence of anti-thyroglobulin antibodies), and adrenocorticotropic hormone (ACTH)/cortisol (for patients with Cushing's disease related to their cancer), before, during, and at the end of treatment (EOT) with selpercatinib.

- To collect patient-reported outcomes (PRO) data to explore disease-related symptoms and health-related quality of life (HRQoL).
- To estimate the time from initial progressive disease (PD1) to subsequent PD (PD2) to explore whether patients continue to benefit from study treatment after disease progression.

3 Investigational Plan

3.1 Study Design

This is an open-label, multi-center Phase 2 study in patients with advanced solid tumors, including *RET* fusion-positive solid tumors (e.g., NSCLC, thyroid, pancreas, colorectal), *RET*-mutant MTC, and other tumors with *RET* activation (e.g., mutations in other tumor types or other evidence of RET activation).

Patients with *RET* alterations in tumor and/or blood will be identified through molecular assays. The *RET* alteration results should be generated from a laboratory with certification by China National Accreditation Service for Conformity Assessment (CNAS), External Quality Assessment (EQA), Clinical Laboratory Improvement Amendments (CLIA), College Of American Pathologists (CAP) or other similar certification. The Sponsor should be contacted to discuss test results to ensure trial eligibility.

The Schedule of Assessments (refer to Table 7-1) consists of a screening period, a treatment period including an End of Treatment (EOT) visit, a Safety Follow-up (SFU) visit, and Long-term Follow-up (LTFU). Ongoing safety, and disease assessments (for patients without PD), disease status, survival, and subsequent anticancer therapy(ies) will be assessed during LTFU.

Selpercatinib will be administered in oral form BID. Dosing will be fixed as total milligram (mg; as opposed to weight-based or body surface area [BSA]-based).

3.2 Length of Study and End of Study

3.2.1 Length of Study

It is anticipated that a patient on this study will receive treatment with open-label selpercatinib until the patient is able to obtain commercially available selpercatinib in China, if the patient does not meet criteria requiring discontinuation of treatment (refer to Section 6.4 Discontinuation of Study Intervention), and the patient's participation in the study has not ended. The study may be terminated if selpercatinib does not obtain marketing approval or the development of selpercatinib is no longer being pursued by the Sponsor. The Sponsor also reserves the right to discontinue the study for clinical or administrative reasons at any time.

3.2.2 End of Study

The end of study is defined as the date when the last remaining patient has:

- Completed the last visit where the patient completed the SFU visit, or
- consent has been withdrawn, or
- is lost to follow-up, or
- has died, or
- has transferred to a separate study to received further medication.

3.3 General Treatment Procedures

Patients will receive 160 mg BID selpercatinib on Cycle (C) 1 Day (D) 1 in accordance with the cohort assignment. Cycles are measured in 28-day increments.

Individual patients will continue daily selpercatinib dosing until PD, unacceptable toxicity, or other reasons for treatment discontinuation, as outlined in Section 6.4. Twenty-eight days after the last dose of study drug (+7 days), all treated patients will undergo an SFU visit. Patients with documented PD may be allowed to continue selpercatinib if the patient is tolerating treatment and, in the opinion of the Investigator, the patient is deriving clinical benefit from continuing study treatment, and continuation of treatment is approved by the Sponsor.

After treatment discontinuation, all patients will enter the LTFU part of the study until death, withdrawal of consent, lost to follow-up or the Sponsor makes a decision to close the study. LTFU will include follow up for survival status, which may be conducted by telephone. During LTFU, for practical reasons and to minimize patient inconvenience, continued disease assessments by imaging until disease progression are optional. For any patient who is lost to follow-up, the study site will attempt to ascertain survival information via public database search. If survival status still cannot be ascertained, patients will be considered lost to follow-up and will be censored appropriately.

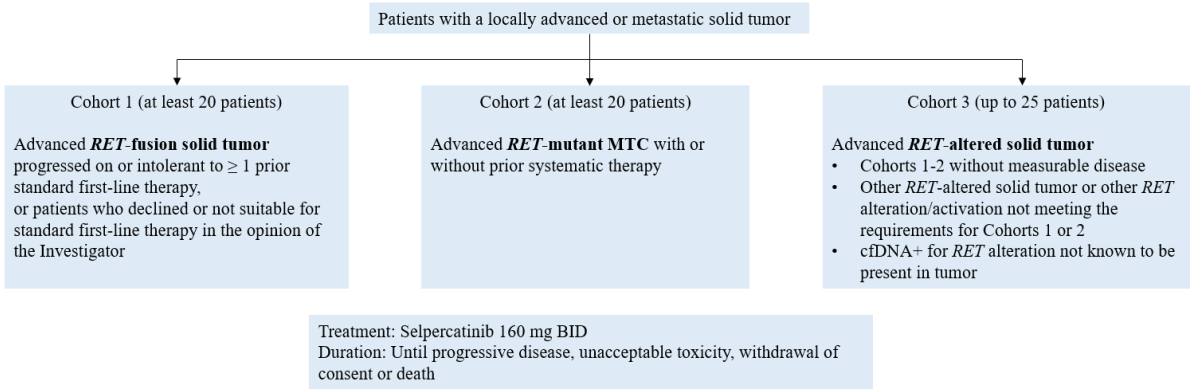
3.4 Investigational Plan

For this China-specific protocol, it is expected that at least 20 patients in each Cohort 1 and Cohort 2, and up to 25 patients in Cohort 3 with advanced solid tumors with evidence of a *RET* gene alteration in tumor and/or blood (e.g., gene rearrangement fusions and/or mutations, excluding synonymous, frameshift, or nonsense mutations) will be enrolled to one of three cohorts (Figure 3-1) as noted below to better characterize the safety and efficacy of selpercatinib in patients with specific abnormalities in *RET*. For Cohort 1 and 2, evidence of a *RET* gene alteration in tumor (i.e., not just blood) as defined in Table 3-1 is required (a positive germline test for a *RET* mutation is acceptable for patients with MTC).

Enrollment will be based on tumor type, type of *RET* alteration, and prior treatment:

- Cohort 1: Advanced *RET* fusion-positive solid tumor progressed on or intolerant to ≥ 1 prior standard therapy, or patients who declined or not suitable for standard first line therapy in the opinion of the Investigator (refer to Table 4-1 for standard therapies). For lung cancer, only patients harboring *RET-KIF5B, RET-CCDC6, RET-NCOA4* can be enrolled in Cohort 1. For other solid tumors, patients with any *RET* fusions can be enrolled in Cohort 1.
- Cohort 2: Advanced *RET*-mutant MTC with or without prior systematic therapy
- Cohort 3: Advanced *RET* altered solid tumor
  - Cohorts 1-2 without measurable disease;
  - Other *RET*-altered solid tumor or other *RET* alteration/activation not meeting the requirements for Cohorts 1 or 2;
  - MTC syndrome spectrum cancers (e.g. MTC, pheochromocytoma) with neuroendocrine features/differentiation or poorly differentiated thyroid cancers with other *RET* alteration/activation may be allowed with prior Sponsor approval;
  - Known cfDNA positive for a *RET* gene alteration and not able to be determined in tumor or FISH positive in tumor without PCR/NGS result may be allowed with prior Sponsor approval.

Selpercatinib will be administered in oral form at 160 mg BID. Each cycle will consist of 28 days.



Primary endpoint: ORR per RECIST 1.1 by independent review committee.

Secondary endpoint: ORR per RECIST 1.1 by investigator, DOR, CNS ORR, CNS DOR, CBR, TTR, TTBR, CBR, PFS, OS, PK, safety

Abbreviations: BID-twice daily, MTC-medullary thyroid cancer, DOR- duration of response, CNS ORR- central nervous system objective response rate, CNS DOR- central nervous system duration of response, CBR- clinical benefit rate, TTR- time to response, TTBR- time to best response, PFS-progression-free survival, OS- overall survival, PK- pharmacokinetic

Figure 3-1 Study Schema

3.5 Definition of *RET* Alterations

The specific *RET* gene alterations required for enrollment to Cohort 1 and 2 are defined in Table 3-1. *RET* mutations and fusions will be identified from a laboratory with CNAS, EQA, CLIA, CAP or similar certification, so long as a written Molecular Pathology Report is available and clearly asserts the presence of the referenced *RET* alteration.

Table 3-1 Definition of *RET* Alterations

RET* mutation
Previously reported activating *RET* gene mutation excluding synonymous, frameshift, or nonsense mutations. Refer to Appendix B (Table 11-2) for examples. For MTC, *RET* gene mutation not known to be activating may be enrolled with Sponsor approval to Cohort 2.
RET* fusion
By PCR or NGS (FISH as the only molecular result is acceptable for Cohort 3, but not Cohort 1).
RET* mutation* or *RET* fusion
No other known validated driver alteration(s). Refer to Appendix C for examples.
* According to laboratory with CNAS, EQA, CLIA, CAP or similar certification, so long as a written Molecular Pathology Report is available and clearly asserts the presence of the referenced *RET* alteration.

Abbreviations: CNAS-China National Accreditation Service for Conformity Assessment; EQA; CLIA-Clinical Laboratory Improvement Amendments; CAP-College Of American Pathologists; FISH-Fluorescence in Situ Hybridization; MTC-medullary thyroid cancer; NGS-next generation sequencing; PCR-polymerase chain reaction.

3.6 Number of Patients

Approximately 75 patients will be enrolled.

A statistical justification of sample/cohort size is provided in Section 9.3.

3.7 Investigational Sites

Approximately 40 institutions will be recruited to enroll patients.

4 Selection of Study Population

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted. Potential patients age 18 and older must sign an informed consent form before any study-specific screening tests may be conducted.

4.1 Inclusion Criteria

1. Patients with a locally advanced or metastatic solid tumor who:
   - have progressed on or are intolerant to standard therapy, or
   - no standard therapy exists, or in the opinion of the Investigator, are not candidates for or would be unlikely to tolerate or derive significant clinical benefit from standard therapy, or
   - decline standard therapy.
2. Prior MKIs with anti-RET activity are allowed. Refer to Appendix A for examples of MKIs with anti-RET activity. However, prior treatment with a selective RET inhibitor(s) (including investigational selective RET inhibitor(s), such as BLU-667, RXDX-105) is prohibited. The specific agent(s), duration of treatment, clinical benefit, and reason for discontinuation (e.g., PD, drug toxicity, or intolerance) should be documented for all kinase inhibitors the patient has been exposed to.
3. Evidence of a *RET* gene alteration in tumor and/or blood (e.g., gene rearrangement and/or mutation, excluding synonymous, frameshift, or nonsense mutations), as identified through molecular assays, as performed for clinical evaluation. The *RET* alteration result should be generated from a laboratory with certification by CNAS, EQA, CLIA, CAP or other similar certification. The Sponsor should be contacted to discuss test results from labs where such certification is not clearly demonstrated to determine eligibility.

   Notes:
   - A positive germline test for a *RET* mutation is acceptable for patients with MTC.
   - Local testing in a CNAS, EQA, CLIA, CAP or other similar certified laboratory is sufficient.
   - In all cases, a redacted/coded Molecular Pathology Report or other report(s) describing tumor and/or blood *RET* (and other) alternation analysis should be submitted to the Sponsor or designee during/prior to eligibility.
4. Measurable or non-measurable disease as determined by RECIST v1.1.
5. At least 18 years of age.
6. Eastern Cooperative Oncology Group (ECOG) performance status score of 0, 1, or 2, with no sudden deterioration 2 weeks prior to the first dose of study treatment.
7. Life expectancy of at least 3 months.
8. Archived tumor tissue sample available for Cohort 1 and 2.

Notes:

- Patients who do not have adequate archival tumor tissue available (refer to specific archival tissue requirements in Section 7.7.5.1) may undergo a fresh tumor biopsy, if it is considered safe to perform, prior to treatment.
- If archived tumor tissue was obtained prior to progression on the last MKI with anti-RET activity, the patient should undergo a fresh tumor biopsy, if it is considered safe to perform, prior to treatment (optional).

9. Adequate hematologic status, defined as:
   - Absolute neutrophil count (ANC) $\geq 1.0 \times 10^9$/L not requiring growth factor support for at least 7 days prior to treatment, and
   - Platelet count $\geq 75 \times 10^9$/L not requiring transfusion support for at least 7 days prior to treatment, and
   - Hemoglobin (Hb) ≥ 9 g/dL not requiring transfusion support or erythropoietin for at least 7 days prior to treatment.
10. Adequate hepatic function, defined as:
    - Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) $\leq 2.5 \times$ the upper limit of normal (ULN) or $\leq 5 \times$ ULN with documented liver involvement (such as liver metastasis or a primary biliary tumor) and
    - Total bilirubin $\leq 1.5 \times$ ULN or $\leq 3 \times$ ULN with documented liver involvement (patients with Gilbert's Disease may be enrolled with prior Sponsor approval).
11. Adequate renal function, with estimated glomerular filtration rate ≥ 30 mL/minute. Sites can use their own clinical standard for eGFR. If no clinical standard, below MDRD study equation can be used: eGFR (mL/min/1.73 m²) = $175 \times (S_{cr}/88.4)^{-1.154} \times (Age)^{-0.203} \times (0.742$ if female) $\times (1.212$ if African American) (SI units).
12. Ability to swallow capsules and comply with outpatient treatment, laboratory monitoring, and required clinic visits for the duration of study participation.
13. Willingness of men and women of reproductive potential to observe conventional and effective birth control for the duration of treatment and for 3 months following the last dose of study treatment; this may include barrier methods such as a condom or diaphragm with spermicidal gel.

    Notes:

    - A postmenopausal woman will be defined as having no menses for 12 months without an alternative medical cause. Male sterility will be defined as only men sterilized surgically. For male patients with a pregnant partner, a condom should be used for contraception. For male patients with a non-pregnant female partner of child-bearing potential and woman of child-bearing potential one of the following birth control methods with a failure rate of less than 1% per year when used consistently and correctly are recommended:
      a. Combined estrogen and progesterone containing hormonal contraception associated with inhibition of ovulation given orally, intravaginally, or transdermally
      b. Progesterone-only hormonal contraception associated with inhibition of ovulation given orally, by injection, or by implant

c. Intrauterine device (IUD)
d. Intrauterine hormone-releasing system (IUS)
e. Bilateral tubal occlusion
f. Vasectomized partner
g. Sexual abstinence

- Birth control methods unacceptable for this clinical trial are:
  a. Periodic abstinence (calendar, symptothermal, or post-ovulation methods)
  b. Withdrawal (coitus interruptus)
  c. Spermicide only
  d. Lactational amenorrhea method
- Male study participants should refrain from sperm donation during study treatment and up to 6 months following the last dose of selpercatinib.

14. Written informed consent and any local required authorization (e.g., Health Insurance Portability and Accountability Act in the US, European Union [EU] Data Privacy Directive in the EU) obtained from the patient/legal representative prior to performing any protocol-related procedures, including screening evaluations.
15. Cohorts 1 and 2: failed or intolerant to standard of care; see Table 4-1 for Examples.

Table 4-1 Standard of Care Therapies for Cohort 1 and 2

Cohort	Therapy
Cohort 1: *RET* Fusion-Positive Solid Tumor	NSCLC: platinum-based chemotherapy (or other chemotherapy if not eligible for platinum) or PD-1/PD-L1 immunotherapy or both Thyroid: sorafenib, patients must also be radioactive iodine-refractory as appropriate Colorectal: fluoropyrimidine-based chemotherapy, with or without anti-VEGF-directed therapy or anti-EGFR-directed therapy as appropriate for the disease Pancreas: fluoropyrimidine-based, gemcitabine-based, or S-1 chemotherapy Breast: anthracycline, taxane, HER2-directed therapy and/or hormonal therapy or other standard therapy appropriate for the disease Other: prior standard therapy for the disease
Cohort 2: *RET*-mutant MTC	No approved SOC

Abbreviations: EGFR-epidermal growth factor receptor; HER2-human epidermal growth factor receptor 2; MTC-medullary thyroid cancer; NSCLC-non-small cell lung cancer; PD-1-programmed cell death protein 1; PD-L1-programmed death-ligand 1; VEGF-vascular endothelial growth factor.

16. Cohorts 1-2: enrollment will be restricted to patients with evidence of a *RET* gene alteration in tumor (i.e., not just blood) as defined in Synopsis Table 1 . However, a positive germline DNA test for a *RET* gene mutation as defined in Appendix B (Table 11-2) is acceptable in the absence of tumor tissue testing for patients with MTC.
17. Cohorts 1-2: at least one measurable lesion as defined by RECIST v1.1 and not previously irradiated (unless PD for the irradiated lesion[s] has been radiographically documented).
18. Cohort 2: radiographic PD within the previous 14 months for systematic treatment naïve patient.

    Note:
    Patients otherwise eligible for Cohort 2 who do not demonstrate radiographic PD within the previous 14 months may be enrolled to Cohort 3 if a compelling rationale is provided by the Investigator and approved by the Sponsor.

4.2 Exclusion Criteria

19. Cohorts 1-2, an additional validated oncogenic driver that could cause resistance to selpercatinib treatment if known. See Appendix C (Table 11-3) for examples.
20. Prior treatment with a selective RET inhibitor(s) (including investigational selective RET inhibitor(s), such as BLU-667, RXDX-105, etc.)
21. Are currently enrolled in any other clinical study involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study
22. Investigational agent or anticancer therapy within 5 half-lives or 2 weeks (whichever is shorter) prior to planned start of selpercatinib. In addition, no concurrent investigational anti-cancer therapy is permitted.

    Notes:

    - Refer to Section 6.3.2 of the main protocol for allowable concurrent therapies.
    - Selpercatinib may be started within less than 5 half-lives or 2 weeks of prior therapy if considered by the Investigator to be safe and within the best interest of the patient, with prior sponsor approval.
23. Major surgery (excluding placement of vascular access or biopsy) within 4 weeks prior to planned start of selpercatinib.
24. Radiotherapy with a limited field of radiation for palliation within 1 week of the first dose of study treatment, with the exception of patients receiving radiation to more than 30% of the bone marrow or with a wide field of radiation, which must be completed at least 4 weeks prior to the first dose of study treatment.
25. Any unresolved toxicities from prior therapy greater than CTCAE Grade 1 except where otherwise noted in this eligibility criteria at the time of starting study treatment with the exception of alopecia and Grade 2, prior platinum therapy-related neuropathy.
26. Symptomatic primary CNS tumor, symptomatic CNS metastases, leptomeningeal carcinomatosis, or untreated spinal cord compression.

Exception: Patients are eligible if neurological symptoms and CNS imaging are stable and steroid dose is stable for 14 days prior to the first dose of selpercatinib and no CNS surgery or radiation has been performed for 28 days, 14 days if stereotactic radiosurgery [SRS].

Note:

- All prior local treatments for CNS disease (e.g. surgery, whole brain radiation [WBRT], SRS), the start and stop dates for each prior local therapy, the specific lesions treated (if SRS and/or surgery), whether the patient developed intracranial progression after the last prior local treatment, and which lesions progressed since completion of the local therapy must be documented.

27. Clinically significant active cardiovascular disease or history of myocardial infarction within 6 months prior to planned start of selpercatinib or prolongation of the QT interval corrected for heart rate using Fridericia's formula (QTcF) > 470 msec. Correction of suspected drug-induced QTcF prolongation may be attempted at the investigator's discretion if clinically safe to do so.
28. History of Human Immunodeficiency Virus (known HIV 1/2 antibodies positive); patients with unknown HIV status do not need to be tested.
29. History of active hepatitis B (known positive hepatitis B surface antigen [HbsAg] and quantitative hepatitis B DNA greater than the upper limit of detection of the assay) or C (known positive hepatitis C antibody and quantitative hepatitis C RNA greater than the upper limit of detection of the assay); patients with unknown hepatitis B/hepatitis C status do not need to be tested.
30. Active uncontrolled systemic bacterial, viral, or fungal infection or serious ongoing intercurrent illness, such as hypertension or diabetes, despite optimal treatment. Screening for chronic conditions is not required.
31. Clinically significant active malabsorption syndrome or other condition likely to affect gastrointestinal absorption of the study drug.
32. Uncontrolled symptomatic hyperthyroidism or hypothyroidism.
33. Uncontrolled symptomatic hypercalcemia or hypocalcemia.
34. Concurrent use of drugs known to prolong QTc (refer to Appendix D of the main protocol)
35. Pregnancy or lactation. Breast-feeding should be interrupted when selpercatinib is started; breast-feeding can be resumed 3 months after discontinuation of selpercatinib.
36. Active second malignancy other than minor treatment of indolent cancers with prior sponsor approval.

5 Enrollment Procedures

For all patients, a copy of the redacted Molecular Pathology Report, or other report(s) describing tumor *RET* (and/or other) alteration analysis must be submitted to the Sponsor or designee during Screening for review prior to patient enrollment.

Individuals who do not meet the criteria for participation in this study (screen failure) may be re-screened, only after discussion with and permission from the Lilly CRP or designee. Patients may be eligible for re-screening up to 2 times in any of the following circumstances:

- Patients who have become eligible to enroll in the study as the result of a protocol amendment.
- Patients whose status has changed such that the eligibility criterion that caused the patient to screen fail would no longer cause the patient to screen fail again.
- Patients who complete screening and meet all inclusion and exclusion requirements but are unable to be enrolled due to extenuating circumstances (such as severe weather, or child illness).

Each time re-screening is performed, the individual must sign a new informed consent form (ICF) and will be assigned a new identification number. If a target gene positive result was obtained for an individual under their first patient number, this result can be linked to their new number in an effort to preserve patient tissue. If a target gene result was not successfully obtained for an individual under their first patient number, then a new sample for this individual (as well as one repeat if needed) can be submitted to the central lab with the new patient number. Repeating of laboratory tests during the screening period does not constitute re-screening.

This is an open-label study, and all patients who meet all criteria for enrollment will receive selpercatinib treatment. Dispensing and tracking selpercatinib treatment will be accomplished using an interactive Web/voice response system (IxRS).

6 Treatment

6.1 Investigational Product

Selpercatinib will be provided in a capsule in 40 mg and 80 mg dose strengths.

6.1.1 Capsules

Selpercatinib will be provided in a capsule in 40 mg and 80 mg dose strengths. The 40 mg capsules will be provided to the sites in bottles of 60 capsules/bottle. The 80 mg capsules will be provided to the sites in bottles of 120 capsules/bottle. The site pharmacist will dispense bottles to the patient in an amount necessary to allow for outpatient administration at the assigned dose level. Dosing is intended to be fixed (i.e., not weight-based or body surface area-based).

Selpercatinib gelatin capsules are to be stored at controlled room temperature in accordance with the labeled storage conditions.

Additional details regarding the investigational product are provided in the selpercatinib Pharmacy Manual and the selpercatinib IB.

6.2 Selpercatinib Administration

6.2.1 General Dosing Instructions

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).

The patient 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) should be noted in the diary. Doses that are late by more than 6 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.

Selpercatinib may be given with or without food, unless the patient requires treatment with PPIs, H2 receptor antagonists, or locally-acting antacids. Additional guidance is provided in Section 6.3.3.

Patients taking these agents are encouraged to record the time of each dose in relationship to each dose of selpercatinib in the dosing diary (inaccurate recording will not be considered a protocol violation).

6.2.2 Cycle 1

Patients will begin dosing on C1D1. Serial blood samples for intensive PK monitoring will be collected for a total of 12 patients, blood samples for population pharmacokinetic (PopPK) will be collected for all enrolled patients, and the patient will be monitored for safety as outlined in Section 7.2 Cycle length is 28 days for all patients.

6.2.3 Cycles 2 and Higher

Patients will receive selpercatinib 160 mg BID in continuous 28-day cycles until PD, unacceptable toxicity, or other reasons for treatment discontinuation. Patients with documented PD may be allowed to continue selpercatinib if the patient is tolerating treatment and, in the opinion of the Investigator, the patient is deriving clinical benefit from continuing study treatment, and continuation of treatment is approved by the Sponsor. Additionally, the patient must reconsent prior to continuing to receive study treatment.

6.2.4 Dose Delays and Modifications

Cycles are 28 days in duration regardless of dose interruption unless toxicity recovery period before entering next cycle includes Day 1 of the next cycle. For patients with dose interruption, next cycle will start with resumption of study drug. In this situation, disease assessments should continue to follow the original schedule.

For all parts of this study, toxicities such as nausea, vomiting, or diarrhea or dizziness or dehydration related to these symptoms, may be managed with increased supportive care, including hydration, electrolyte repletion and the use of anti-emetics such as serotonin type 3 (5-HT3) antagonists and/or anti-diarrheals such as loperamide as appropriate.

Treatment for the first cycle should commence only if all the inclusion and exclusion criteria are met. Subsequently, the selpercatinib dose may be delayed/modified if the patient experiences a Grade 3 or greater clinical AE considered to be at least possibly related to selpercatinib.

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 adverse events or Grade 2 adverse events 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 specific adverse events (hypersensitivity, liver function test abnormalities, thrombocytopenia, and hypertension), see dose adjustments below in Sections 6.2.3 (any concerns of these recommended actions in clinical practice should be discussed with the Sponsor, who may permit adjust actions).
- Dose modifications for ECG changes are described in Section 8.2.1. If a patient receiving selpercatinib experiences QTCF > 500 msec despite two dose reductions and if the investigator deems it in the best interest of the patient, the patient may continue treatment with study drug with CRP/CRS approval. In addition, Lilly may request a copy of the ECGs for adjudication.
- Upon resolution (or return to patient's baseline) of adverse events 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 not permitted (other than hypersensitivity, liver test abnormalities, thrombocytopenia, and hypertension).

Permanently discontinue treatment for any of: malignant hypertension, hypertensive crisis, or persistent uncontrolled hypertension despite optimal medical management. Patients with clinical benefit who experience recurrent hypersensitivity reaction or recurrent AST or ALT increase despite dose reductions should be discussed with the CRS/CRP 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.

Before the start of each cycle, Grade 3 hematologic toxicity possibly related to selpercatinib must resolve to either baseline or at least Grade 2. If a patient experiences Grade 4 hematologic toxicity possibly related to selpercatinib, then dosing must be suspended (until the toxicity resolves to either baseline or at least Grade 2) and the dose of selpercatinib must be reduced as outlined in Table 6-1.

Before the start of each cycle, nonhematologic toxicity (except AEs with no immediate medical consequence that can be controlled with adequate treatment (e.g. pain, alopecia, neuropathy fatigue, nausea, vomiting, diarrhea, Grade 2 hypothyroidism, or Grade 2 hypertension).) possibly related to selpercatinib must resolve to either baseline or at least Grade 1. If a patient experiences persistent or recurrent Grade 2 nonhematologic toxicity possibly related to selpercatinib that does not resolve with maximal supportive measures within 7 days to either baseline or Grade 1, then dosing may be suspended (until the toxicity resolves to either baseline or at least Grade 1) and the dose of selpercatinib may be reduced as outlined in Table 6-1.

Treatment may be delayed for a maximum of 28 days to allow a patient sufficient time for recovery from selpercatinib-related toxicity. If a patient does not recover from the toxicity within 28 days from the time of last treatment, the patient must be discontinued from selpercatinib. In rare circumstances, a delay >28 days may be permitted before discontinuing the patient from treatment, as long as the patient demonstrates clinical benefit without objective progression and is recovering from the toxicity. Such circumstances should be discussed between Sponsor and Investigator and documented.

Table 6-1 Suggested Toxicity Management for all Parts of this Study

Dose Level	**Dose of Selpercatinib**
Starting Dose	160 mg BID
First Dose Reduction	120 mg BID*
Second Dose Reduction	80 mg BID*
Third Dose Reduction and Beyond	Only permitted if there is a compelling clinical rationale articulated by the Investigator and approved by the Sponsor.

Abbreviations: AE-adverse events; BID-twice daily; LFT-liver function test.

*For the specific AEs of hypersensitivity reactions, LFT increases, thrombocytopenia and hypertension, the Sponsor may recommend a lower starting dose (i.e. 40 mg BID for hypersensitivity reactions and 80 mg BID for certain LFT increases, 120 mg BID for thrombocytopenia) upon resumption of study drug treatment, with subsequent dose escalation if tolerated without clinically significant recurrence of the AEs. Occurrence of these AEs should be discussed with the Sponsor.

All dose interruptions and dose modifications and the reasons for those changes will be recorded in the electronic Case Report Form (eCRF).

Guidance for Investigator on Specific Adverse Events

Dose Modifications for Selpercatinib Hypersensitivity

Please refer to the IB for the most current guidance on management of selpercatinib hypersensitivity reactions. Recommended actions are shown below.

If selpercatinib drug hypersensitivity is suspected, study drug should be withheld 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 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. Follow the guidelines below if hypersensitivity recurs:

- If recurrence is severe, selpercatinib should again be withheld.
- If recurrence is mild (e.g., isolated instances of rash or myalgias or low-grade fever), selpercatinib may be continued cautiously, together with treatment with supportive therapy (e.g., topical treatments, ibuprofen).
- If the patient experiences a clinically significant recurrence of drug hypersensitivity at the initial re-exposure dose of 40 mg BID, selpercatinib should be discontinued.

After a minimum of 7 days and 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. Once the patient has tolerated treatment for a minimum of 7 days at the final dose, steroids may be tapered slowly.

Dose Modifications for Selpercatinib Related Liver Function Test Abnormalities

If a patient experiences ≥Grade 3 elevated liver function tests (LFTs; including AST, ALT, ALP and total and direct bilirubin), study drug should be withheld and evaluation for potential alternative causes should be conducted (e.g., history of other hepatotoxic medications/ substances, viral serologies, liver imaging). A repeated value 3 to 5 days after the initial finding of elevation of LFTs should be obtained to confirm the abnormality and to confirm if it is increasing or decreasing. Thereafter, LFTs should be monitored at least weekly until resolution to normal/baseline (depending on the clinical situation, resolution to Grade 1 if baseline is acceptable but waiting until normalization is preferable). If the LFT 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.

Upon resolution, for patients who received 160 mg BID or 120 mg BID, the selpercatinib dose should be reduced by 2 dose levels (80 mg BID or 40 mg BID, respectively) with weekly LFTs monitoring. In the absence of recurrent LFT abnormalities, the dose of selpercatinib may be escalated sequentially to the next highest dose (120 mg BID or 80 mg BID, respectively) after a minimum of 2 weeks and again to the original dose and after a minimum of an additional cycle. Once the patient has been treated at a stable dose of selpercatinib for a minimum of 1 cycle without recurrent LFT abnormalities, the frequency of LFTs monitoring may be decreased (e.g., midcycle for 2 cycles and then at the start of every cycle thereafter).

For patients who experience ≥Grade 3 elevated LFTs at 80 mg BID, the sponsor should be contacted for additional guidance regarding dose modification. If the patient experiences ≥Grade 3 elevated LFTs 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.

Dose Modifications for Thrombocytopenia

If a patient is discovered to have thrombocytopenia ≥Grade 3, study drug should be withheld, 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 complete blood count (CBC) testing until the event resolves and CBC level returns to normal/baseline. Upon recovery, the patient should resume selpercatinib with a dose reduction of at least 1 level with weekly CBC surveillance for 1 full cycle.

Dose Modifications for Hypertension

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 antihypertensive medication regimen is initiated, or
- a preexisting 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. Dose re-escalation to the patient's original dose can be considered once adequate blood pressure (BP) control has been obtained; with clinically appropriate monitoring.

6.3 Concomitant Medications

6.3.1 General

All medications that were used from the time that written informed consent has been obtained through the SFU visit (at least 28 days [±7 days] after the last dose of study drug) will be recorded in the eCRF. These are to include prescription and nonprescription medications, transfusions, vitamins, and nutritional supplements, and other remedies. Additional prior excluded medications are indicated in the Exclusion Criteria (Section 4.2).

6.3.2 Allowed Concomitant Medications

Standard supportive medications may be used in accordance with institutional guidelines and Investigator discretion. These may include hematopoietic growth factors to treat neutropenia, anemia or thrombocytopenia (in countries where hematopoietic growth factors are approved for use) in accordance with American Society for Clinical Oncology guidelines (but not for prophylaxis in C1); RBC and platelet transfusions, anti-emetic, analgesic and antidiarrheal medications; electrolyte repletion (e.g., calcium and magnesium) to correct low electrolyte levels; conditional use of steroids treatment as indicated in Section 6.3.3; thyroid replacement therapy for

hypothyroidism; and bisphosphonates, denosumab; and other medications for the treatment of osteoporosis, prevention of skeletal-related events from bone metastases, and /or hypoparathyroidism. Continuation of standard of care medications, including adjuvant hormonal therapy for patients with 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 Section 6.3.3 and Appendix D).

Local treatment while receiving selpercatinib (e.g., palliative radiation therapy or surgery for bone metastases) is permitted with Sponsor approval; however, the Sponsor recommends holding selpercatinib for approximately 5 half-lives (approximately 2 to 3 days) before and after radiation therapy or surgery. Any concern for disease flare due to a prolonged period off from selpercatinib should be discussed with the Sponsor, who may permit holding selpercatinib for a shorter period of time.

6.3.3 Other Concomitant Medications

As selpercatinib is a substrate of CYP3A4, patients should avoid taking strong or moderate inhibitors or inducers of CYP3A4 as they could alter the drug's PK. If concomitant use of strong and moderate CYP3A inhibitors cannot be avoided, reduce the selpercatinib dosage and monitor the QT interval with ECGs more frequently.

Since selpercatinib is more soluble in an acidic environment than a neutral one, absorption may be impacted by stomach acidity, and concomitant use of pH altering agents require additional instructions. The concomitant use of PPIs should be avoided, and patients must take selpercatinib with food (at least 400 calories) when coadministered with a PPI if concomitant use cannot be avoided (refer to Appendix E).

When concurrent use of an H2 blocking agent is necessary, e.g., ranitidine (Zantac®), famotidine (Gaster®), or cimetidine (Tagamet®), it must be administered only 10 hours before or 2 hours after the dose of selpercatinib.

When concurrent use of an antacid is necessary, e.g., aluminum hydroxide/magnesium hydroxide/simethicone (Maalox®) or calcium carbonate (TUMS®), it must be administered 2 hours before and/or 2 hours after the dose of selpercatinib.

Chronic treatment (>7 days) with steroids is not permitted except to treat symptoms from an immune-related AE or brain metastases. Intermittent use of inhaled steroids for asthma or local steroid injections is allowed. Similarly, limited use of systemic corticosteroids (≤7 days) is permitted where it is considered SOC (e.g., as premedication for contrast allergy or for chronic obstructive pulmonary disease exacerbation). Replacement doses of steroids (e.g., prednisone 10 mg daily) are permitted while on study.

In addition, except as indicated in Section 6.3.2, patients are not allowed to receive concomitant systemic anti-cancer agents (including herbal products with anti-cancer activity), hematopoietic growth factors for prophylaxis in C1, therapeutic monoclonal antibodies, radiation therapy (palliative radiation therapy is permitted with Sponsor approval), drugs with immunosuppressant properties, or any other investigational agents besides selpercatinib. No new, alternative systemic anticancer therapy is allowed prior to documentation of PD in accordance with protocol-specified disease response criteria. If during the study, patients require initiation of treatment with strong inhibitors or inducers of CYP3A4 for clinical reasons, then the Sponsor should be consulted to determine whether selpercatinib should be stopped, and therefore whether the patient should be removed from the study. Strong and moderate inhibitors or inducers of CYP3A4 should be taken with caution. If concomitant use of strong and moderate CYP3A inhibitors cannot be avoided, reduce the selpercatinib dosage and monitor the QT interval with ECGs more frequently. Any exceptions to the above must be approved by the Sponsor.

6.3.4 Contraindications

Selpercatinib is contraindicated in patients with known hypersensitivity to any of its capsule components.

6.4 Discontinuation of Study Intervention

Patients will be advised that they are free to discontinue study treatment at any time and that they will be followed for survival after discontinuing treatment (refer to Section 7.6). Over the course of the study, the Investigator and/or the Sponsor should remove a patient from treatment for any of the reasons listed below:

- PD
  Exception: Patients with documented PD who are tolerating treatment and, in the opinion of the Investigator, are deriving clinical benefit from continuing study treatment, may continue treatment with prior Sponsor approval.
- Unacceptable toxicity
- Intercurrent illness compromising ability to fulfill protocol requirements
- Pregnancy
- Requirement for alternative treatment in the opinion of the Investigator, unless such treatment is temporary (e.g., local radiation or surgery for disease that does not meet the definition of PD)
- Significant noncompliance with protocol
- Withdrawal of consent by the patient
- Lost to follow-up
- Death
- Study terminated by Sponsor

Participants discontinuing from the investigational product for any reason should complete adverse event per Table 7-1 (Schedule of Activities), Section 8.2 (Safety Assessments) of the protocol.

At the time a patient discontinues treatment, all safety data normally required at the EOT visit will be obtained if possible, as outlined in Section 7.4. Patients will enter LTFU where they may be required to undergo disease assessments (refer to Section 7.6).

6.4.1 Discontinuation of Inadvertently Enrolled Patients

If Lilly or the investigator identifies a patient who did not meet enrollment criteria and was inadvertently enrolled, a discussion must occur between the Lilly CRP and the investigator to determine if the patient may continue in the study. If both agree it is medically appropriate to continue, the investigator must obtain documented approval from the Lilly CRP to allow the inadvertently enrolled patient to continue in the study with or without study drug. Patients who are discontinued from study drug will have follow-up procedures performed as shown in the Schedule of Activities (Table 7-1).

6.5 Discontinuation/ Withdraw from the Study

Discontinuation from the Study and reasons for end of study could be:

- Withdrawal of consent by the patient
- Lost to follow up
- Death
- Study terminated by Sponsor

Patients who are discontinued from the study will have follow-up procedures performed as shown in the Schedule of Activities.

6.6 Lost to Follow-Up

A patient 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. Study site personnel are expected to make diligent attempts to contact patients who fail to return for a scheduled visit or who the site is otherwise unable to follow-up.

Study site personnel, or an independent third party, will attempt to collect the survival status for all enrolled patients who are lost to follow-up, including enrolled patients who do not receive study drug, within legal and ethical boundaries. Public sources may be searched for survival status information. If the patient's survival status is determined, the survival status will be documented, and the patient will not be considered lost to follow-up.

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

7 Tests and Evaluations

All required observations and their schedules are summarized in Table 7-1 and are described in more detail in the following subsections.

RET alternation from Cohort 1 and 2 will be confirmed centrally. Special assessments, such as PK, will be performed centrally. Additional information regarding handling and processing of these special samples is provided in the separate Laboratory Manual.

Routine laboratories, for example serum chemistries, hematology, and urinalysis, will be performed locally. For each thyroid cancer patient, tests for calcitonin and CEA (MTC patients) and thyroglobulin (non-MTC thyroid cancer patients) should be performed in the same laboratory to minimize intra-patient, lab-to-lab variability in their measurement.

Unless otherwise noted, the routine laboratories and procedures will be performed prior to dosing as noted, and routine evaluations performed within -2 days of the visit day will not be considered protocol deviations.

During the conduct of this study, the Sponsor must be notified of the collection of samples outside of this protocol for separate institutional investigations.

Table 7-1 Schedule of Activity (SoA)

Visit Window	Screening	Cycle 1				Cycle 2-higher	SFU [b]		LTFU [c]
	Up to 28 days prior to first dose	D1 ±2 Days	D8 ±2 Days	D15 ±2 Days	D22 [d] ±2 Days	±2 Days	EOT [a] ⩽ 7 days	D 28 ±7 days	
Informed Consent [e]	X								
Inclusion/exclusion criteria	X								
Medical, surgical, malignancy history	X								
Molecular Pathology Report(s) describing RET and other alterations [f]	X								
Archived tumor tissue or fresh biopsy [g]	X								
Physical examination and ECOG [h]	X	X	X	X		D1 C2, 3, 4, 5, etc.	X	X	
Vital signs [i]	X	X[j]	X[j]	X[j]		D1 C2, 3, 4, 5, etc.	X	X	
12-lead ECG [k]	X	X	X			D1 C2-6 and every 12 weeks	X	X[l]	
Urine or serum pregnancy test [m]	X	X				D1 C2, 3, 4, 5, etc.			
Hematology [n]	X	X	X	X		D1 C2, 3, 4, 5, etc.	X	X	
Serum chemistries [o]	X	X	X	X		D1 C2, 3, 4, 5, etc.	X	X	
Liver function tests [p]						C2D15 and C3D15			

Visit Window	Screening	Cycle 1				Cycle 2-higher	SFU [b]		LTFU [c]
	Up to 28 days prior to first dose	D1 ±2 Days	D8 ±2 Days	D15 ±2 Days	D22 [d] ±2 Days	±2 Days	EOT [a] ⩽ 7 days	D 28 ±7 days	
Coagulation [q]	X	X							
Thyroid panel [r]	X			X		D1 of odd cycles beginning with C3 (C3, 5, 7, etc.)			
Urinalysis [s]	X			X		D1 C2, and as clinically indicated.	X	X	
Calcitonin, CEA (MTC only) [t]	X	X		X		D1 C2 and odd-numbered cycles, starting with C3 through C13. Every 12 weeks thereafter (±7 days of each radiologic disease assessment)	X		
Thyroglobulin (non-MTC thyroid cancers only) [u]	X	X		X		D1 C2 and odd-numbered cycles, starting with C3 through C13. Every 12 weeks thereafter (±7 days of each radiologic disease assessment)	X		
Blood cortisol, ACTH, 24-hour urine for free cortisol [v]	X	X		X		D1 C2 and odd-numbered cycles, starting with C3 through C13. Every 12 weeks thereafter (±7 days of each radiologic disease assessment)	X		
Disease assessment [w]	X					Perform assessments at week 4 (±7 days, optional) and week 8 (±7 days) and then every 8 weeks (±7 days) until week 48 following C1D1 and then every 12 weeks (±7 days)	X [x]		X [y]
Confirmatory disease assessment [z]						At least 4 weeks post 1st PR			
Blood sample for intensive PK [aa]		X	X						
Blood sample for PopPK [bb]		X				D1 of each cycle Predose sample to be drawn			
EORTC QLQ-C30 [cc]		X				Every 8 weeks (±7 days) starting with D1 C3 through D1 C13. Every 12 weeks (±7 days) thereafter	X		

Visit Window	Screening	Cycle 1				Cycle 2-higher	SFU [b]		LTFU [c]
	Up to 28 days prior to first dose	D1 ±2 Days	D8 ±2 Days	D15 ±2 Days	D22 [d] ±2 Days	±2 Days	EOT [a] ⩽ 7 days	D 28 ±7 days	
Dispense selpercatinib		X				D1 of each cycle			
Selpercatinib administration		→	→	→	→	→			
Patient dosing diary		→	→	→	→	→			
Patient bowel diary (MTC only) [dd]		X	X	X	X	D1 C2, 3, 4, 5, etc.	X		
Adverse events [ee]	→	→	→	→	→	→	→	→	
Concomitant medications [ff]	→	→	→	→	→	→	→	→	
Survival [gg]								X	X

Abbreviations (for Table 7-1 and Footnotes): ACTH-adrenocorticotropic hormone; AE-adverse event; ALP-alkaline phosphatase; ALT-alanine aminotransferase; AST-aspartate aminotransferase; BUN blood urea nitrogen; C-cycle; CEA carcinoembryonic antigen; CR complete response; CT-computed tomography; D-day; ECG electrocardiogram; ECOG-Eastern Cooperative Oncology Group; EORTC QLQ-C30-European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EOT-End of Treatment; IV intravenous; LDH lactate dehydrogenase; LTFU long-term follow up; MTC medullary thyroid cancer; MRI magnetic resonance imaging; PD-progressive disease; PK pharmacokinetics; PR partial response; RBC-red blood cell; SAE-serious adverse event; SFU safety follow-up; TSH-thyroid-stimulating hormone; T3-free triiodothyronine; T4-free thyroxine; WBC white blood cell.

a. End of Treatment (EOT): +7 days of the last dose or the decision to terminate treatment. If lab testing is performed ≤7 days prior to EOT, repeat testing does not need to occur on EOT.

b. Safety Follow-Up (SFU): 28 days (±7 days) after last dose of study drug.

c. Long-Term Follow-Up (LTFU): approximately every 3 months (±1 month) for up to two years after the last dose of study drug.

d. Telephone contact for safety.

e. Patient must reconsent prior to continuing to receive study treatment beyond progression.

f. For all patients, redacted report(s) to be submitted to Sponsor or designee during Screening /prior to enrollment.

g. Adequate availability of archived tumor tissue should be confirmed, either tumor block (preferred) or ~10 × 5µm unstained slides should be provided. Patients who do not have sufficient archival tumor tissue available should undergo an optional fresh tumor biopsy, if it is considered safe to perform, prior to

treatment. If sufficient archived tumor tissue is not available and a fresh biopsy cannot be safely performed, the patient may still be eligible with prior Sponsor approval.

h. Physical examination of and review of relevant systems at Screening, body weight, and height. Symptom-directed physical examinations, including measurement of weight may be performed at other time points.

i. Systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature.

j. Vital signs should be conducted as follows:

- C1D1, C1D8: pre-dose (up to 4 hours pre-dose, as close to dosing as possible is preferred) and post-dose at 2 hours (±30 minutes). Vital signs should be performed prior to collection of PK blood sample drawn at that time point.
- C1D15, Day 1 of C2-higher: pre-dose (up to 4 hours pre-dose, as close to dosing as possible is preferred);

k. Obtain a single pre-dose ECG during Screening and again on C1D1. If the C1D1 pre-dose QTcF > 470 msec (QTcF = QT (msec)/RR1/3), where RR (msec) = 60*1000/BPM), the Sponsor should be notified prior to dosing to determine whether the patient remains eligible. On C1D8, C2D1 and thereafter, perform a single ECG at 2 hours (± 10 minutes) post-selpercatinib dosing. On C1D8 PK collection, an extra ECG should be timed prior to the PK sample being drawn. Dose patients in the visit to ensure accuracy of timing. If any ECG demonstrates QTcF 481-500 msec, perform an additional ECG at the same day, specific time judged by investigator. If any ECG demonstrates QTcF > 500 msec, repeat the ECG twice (triplicate in total) at the same day, specific time judged by investigator, and manually review to confirm accuracy. If QTcF > 500 msec is confirmed on 2/3 ECGs, hold selpercatinib and assess for alternative causes (concomitant medications, electrolyte abnormalities). Potassium should be > 4 mEq/L and < ULN and magnesium and calcium should be within normal limits. selpercatinib may be resumed at one reduced dose level when QTcF has returned to baseline value, and with continued ECG monitoring as noted in the assessment schedule.

l. Repeat only if EOT reading showed treatment-emergent abnormalities.

m. For women of childbearing potential: Serum pregnancy test at Screening, serum or urine pregnancy test at Day 1 of every cycle (-2 days) (surgically sterilized females or those who have not experienced menses for at least 2 years are not required to be tested i.e., post-menopausal women who have not had menses within the last 12 months but have had menses within the last 24 months will be required to have a serum pregnancy test performed.). If screening testing is performed ≤7 days prior to C1D1, repeat testing does not need to occur on C1D1.

n. Hemoglobin, hematocrit, RBC count, WBC count with differential (neutrophils [count and percent] and lymphocytes, monocytes, eosinophils, basophils [percent]), and platelet count). Patients found to have treatment-emergent hematologic toxicity of Grades 3 or 4 will be monitored at least weekly until resolution. If screening testing is performed ≤7 days prior to C1D1, repeat testing does not need to occur on C1D1.

o. Detailed serum chemistries (non-fasting) please see appendix H. Note number: ⩽14 days before pre-dose on screening period. If screening testing is performed ≤7 days prior to C1D1, repeat testing does not need to occur on C1D1. Patients found to have treatment-emergent laboratory toxicity of Grades 3 or 4 will be monitored at least weekly until resolution.

p. Collect AST, ALT, ALP, and total and direct bilirubin on C2D15 and C3D15 (±2 days).

q. Additional assessments may be obtained at the discretion of the investigator. If screening testing is performed ⩽7 days prior to C1D1, repeat testing does not need to occur on C1D1.

r. If screening testing is performed ≤7 days prior to C1D1, repeat testing does not need to occur on C1D1. Thyroid-stimulating hormone (TSH), free triiodothyronine (FT3), and free thyroxine (FT4).

s. If screening testing is performed ≤7 days prior to C1D1, repeat testing does not need to occur on C1D1. Detailed urinalysis please see appendix H.

t. If screening testing is performed ≤7 days prior to C1D1, repeat testing does not need to occur on C1D1. Calcitonin and CEA only for patients with a diagnosis of MTC. These should be performed in the same laboratory to minimize intra-patient, lab-to-lab variability in their measurement.

u. If screening testing is performed ≤7 days prior to C1D1, repeat testing does not need to occur on C1D1. Thyroglobulin only for patients with non-MTC thyroid cancers (unless not measurable due to the presence of anti-thyroglobulin antibodies). These should be performed in the same laboratory to minimize intra-patient, lab-to-lab variability in their measurement.

v. If screening testing is performed ≤7 days prior to C1D1, repeat testing does not need to occur on C1D1. Optional for MTC or other cancer patients with Cushing's disease related to their cancer. If performed, urine collection should begin pre-dose. If blood cortisol, ACTH cannot be measured locally, central laboratory will be used to perform the test.

w. Baseline disease assessment with radiographic tumor measurements using CT or MRI of chest, abdomen, and pelvis; And any other areas with suspected disease involvement within 28 days of C1D1 as clinically indicated. Brain imaging is required at baseline for all RET fusion-positive patients, patients with a history of CNS metastases, or other patients if clinically indicated and subsequent serial scans if brain metastases are present at baseline (MRI preferred, CT with contrast is acceptable if MRI contraindicated). Required only for patients with nonmeasurable bone disease identified at baseline or if clinically indicated. For each modality, IV and oral contrast should be utilized unless there is a clear contraindication (e.g., decreased renal function or allergy that cannot be addressed with standard prophylactic treatments). In the absence of known or suspected disease involvement, head and neck CT/MRI scans are not required for malignancies other than those originating in the head and neck region. Other areas of scanning may also differ depending on disease type. Post-baseline scans should be performed every 8 weeks (±7 days) until week 48 and every 12 weeks (±7 days) thereafter, including imaging of the chest, abdomen, and pelvis, using the same modality(ies) as used for baseline imaging assessment until PD, withdrawal of consent, or initiation of a new anticancer therapy(ies). Additionally, any studies performed at baseline that are positive for sites of disease should be repeated at all post-baseline assessments. Additional studies can also be performed as clinically indicated. In addition, Investigators may conduct an initial tumor evaluation on week 4 (±7 days) and a confirmatory tumor evaluation a minimum of 4 weeks (i.e., 28 days) after the first tumor evaluation that shows a CR or PR by RECIST 1.1, if consistent with local regulatory authority requirements. In addition, an initial post baseline assessment on week 4 (±7 days) is encouraged if consistent with regulatory guidelines. If a scan is performed on week 4, the next scan should continue according to the schedule above (beginning at week 8). For patients who continue to receive study treatment beyond progression, post PD scans to determine tumor disease assessment should be performed within 8 weeks (±7 days) of initial PD (PD_1) and every 8 weeks (±7 days) thereafter until subsequent PD (PD_2), withdrawal of consent, or initiation of a new anticancer therapy(ies). Additional scans can be performed as needed. All scans (including any unscheduled scans performed during the study) will be collected and stored at a central facility to permit central reviewer assessment. Please see the Site Imaging Manual for guidelines on how the various imaging studies should be performed.

x. If not performed within the last 8 weeks.

y. Patients who discontinue study drug for reasons other than PD (e.g., AE, noncompliance, etc.) may (but for practical reasons and to minimize patient inconvenience, are not required to) undergo additional disease assessment by imaging (as specified above until PD, withdrawal of consent or initiation of a new anticancer therapy(ies)).

z. Confirmatory scans: Minimum of 4 weeks (e.g., 28 days) after the first tumor evaluation showing a CR or PR by RECIST 1.1, if permitted by regulatory authorities. The next scan should continue according to the schedule above.

aa. For 12 subjects in intensive PK testing, PK test performed on C1D1: Up to pre-dose, and post-dose 1 hour (±15 minutes), 2 hours (±15 minutes), and 4 hours (±15 minutes), 8 hours (±30 minutes) and 12 hours (±30 minutes), C1D8: Up to pre-dose, and post-dose 1 hour (±15 minutes), 2 hours (±15 minutes), and 4 hours (±15 minutes) and 8 hours (±30 minutes).

bb. For all enrolled subjects in PopPK testing, PK test performed on each cycle D1 predose.

cc. EORTC QLQ-C30. The questionnaires should be answered by the subject to the best of his/her ability, prior to receiving drug on C1D1 and preferably prior to learning the results of the radiologic disease assessment for subsequent cycles.

dd. Only for patients with a diagnosis of MTC and diarrhea at baseline. Two patient bowel diary cards will be dispended on C1D15. The questionnaires should be answered by the subject to the best of his/her ability.

ee. AEs and SAEs should be recorded from the time that written informed consent has been obtained through the SFU Visit.

ff. Concomitant, ongoing medication(s) plus those administered within 14 days prior to the planned start of treatment.

gg. Patients will be followed for survival status, date of progression, and subsequent anticancer therapy(ies) by telephone or other method.

7.1 Screening Period

The following procedures must be obtained within 28 days of C1D1 unless otherwise noted. Patients who cannot complete the procedures within the screening window may be rescreened, and certain screening procedures, in investigator's opinion, may not need to be repeated, including certain procedures that were obtained as part of the patient's standard care prior to providing informed consent for this study (provided the patient provides informed consent), with the approval of the Sponsor.

- Informed Consent.
- Medical, surgical, and malignancy history, including histologic confirmation of solid tumor, primary and metastatic diagnosis dates, prior treatments for the malignancy, etc.
- Submission of redacted Molecular Pathology Report(s) describing *RET* and other alterations, to Sponsor or designee.
- Confirmation of availability of archived tumor tissue to be submitted, either tumor block (preferred) or ~10 × 5µm unstained slides. If archived tumor tissue is not available or is of insufficient quantity or quality, a fresh tumor biopsy could be obtained prior to selpercatinib. If patients cannot provide sufficient tumor tissue sample, patients still can be enrolled after discussion between sponsor and investigator and get sponsor's approval. Physical examination, including relevant review of systems, body weight and height, and ECOG performance status (refer to Appendix F).
- Vital signs, including systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature.
- Obtain a single ECG during Screening.
- Serum pregnancy test for women of childbearing potential (surgically sterilized females or those who have not experienced menses for at least 2 years are not required to be tested i.e., post-menopausal women who have not had menses within the last 12 months, but have had menses within the last 24 months will be required to have a serum pregnancy test performed.).
- Hematology, details described in Appendix H.
- Serum chemistries (non-fasting), details described in Appendix H.
- Coagulation: (as described in Section 7.1).
- Thyroid panel, including thyroid stimulating hormone (TSH), free triiodothyronine (FT_3), and free thyroxine (FT_4).
- Urinalysis, details described in Appendix H.
- Calcitonin, CEA: for patients with MTC only. For each patient, all tests for calcitonin and CEA should be performed in the same laboratory to minimize intra-patient, lab-to-lab variability in their measurement.
- Thyroglobulin: for patients with non-MTC thyroid cancers only (unless not measurable due to presence of anti-thyroglobulin antibodies). For each patient, all tests for

thyroglobulin should be performed in the same laboratory to minimize intra-patient, lab-to-lab variability in their measurement.

- Blood cortisol, adrenocorticotropic hormone (ACTH), 24-hour urine for free cortisol: optional for patients with Cushing's disease related to their cancer.
- Baseline disease assessment with radiographic tumor measurements using:
  - All patients: computerized tomography (CT) or magnetic resonance imaging (MRI) of chest, abdomen, and pelvis, and any other areas with suspected disease involvement, within 28 days of C1D1.

    Note: Accurate documentation of prior irradiation including exact locations/sites must be provided.
  - All fusion-positive solid tumor patients, patients with a history of CNS metastases, or other patients if clinically indicated: brain imaging, MRI with and without contrast is preferred, CT with and without contrast is acceptable if MRI is medically contraindicated, within 28 days of C1D1.
  - For each modality, intravenous (IV) and oral contrast should be utilized where applicable unless medically contraindicated.
  - If CT/positron emission tomography (PET) is utilized, the CT component of CT/PET must be of the same quality as a dedicated diagnostic CT scan, i.e., with IV and oral contrast and 5 mm or less slice thickness.
  - Bone scan required only for patients with nonmeasurable bone disease identified at baseline or if clinically indicated.

    Notes:

    – In patients with thyroid and other head and neck cancers, imaging of the relevant areas (e.g., neck, skull base) is required at baseline; other areas of scanning may differ depending on disease type. Refer to the separate Imaging Manual that will be distributed to the sites for details.
    – Additional scans can be performed as needed to evaluate potential sites of disease.
    – Disease assessments will utilize RECIST 1.1 (refer to Section 7.7.1).
    – Guidelines on the technical parameters of how scans should be performed will be provided in the Imaging Manual
- Concomitant, ongoing medications plus those administered within 14 days prior to the planned start of treatment.

7.2 Cycle 1

The procedures listed below will be performed at the indicated intervals. Observations, routine laboratory tests, and HRQoL assessments will be performed prior to selpercatinib dosing on that day unless otherwise indicated. Routine clinic visits and C1D1 evaluations performed within -2 days of the nominal visit day will not be considered protocol deviations, with the exception of ECGs, PKs, and vital signs, which must be performed relative to the dose of selpercatinib on that day as indicated below.

Day 1

- Symptom-directed physical examination, weight, and ECOG.
- Vital signs: pre-dose (up to 4 hours pre-dose, as close to dosing as possible is preferred) and 2 hours post-dose (±30 minutes). Vital signs should be performed prior to collection of PK blood sample drawn at that time point.
- Resting 12-lead ECG: pre-dose (up to 4 hours pre-dose).
- Serum or urine pregnancy test for women of childbearing potential (surgically sterilized females or those who have not experienced menses for at least 2 years are not required to be tested i.e., post-menopausal women who have not had menses within the last 12 months, but have had menses within the last 24 months will be required to have a serum pregnancy test performed).
- Hematology (as described in Appendix H).
- Serum chemistries (as described in Appendix H).
- Blood sample of intensive PK (2 mL whole blood) for a total 12 subjects: pre-dose, and post-dose at 1 hour (±15 minutes), 2 hours (±15 minutes), and 4 hours (±15 minutes), 8 hours (±30 minutes) and 12 hours (±30 minutes). Exact clock time (24h format) of sample collection and of dose administration should be recorded.
- Blood sample of PopPK (2 mL whole blood) for all enrolled subjects: each cycle D1 predose.
- Coagulation (as described in Section 7.1).
- Calcitonin, CEA: for patients with MTC only. For each patient, all tests for calcitonin and CEA should be performed in the same laboratory to minimize intra-patient, lab-to-lab variability in their measurement.
- Thyroglobulin: for patients with non-MTC thyroid cancer only (unless not measurable due to presence of anti-thyroglobulin antibodies). For each patient, all tests for thyroglobulin should be performed in the same laboratory to minimize intra-patient, lab-to-lab variability in their measurement.
- Blood cortisol, ACTH, 24-hour urine for free cortisol: optional for patients with Cushing's disease related to their cancer. If done, urine collection should begin pre-dose.
- Dispense selpercatinib.
- Selpercatinib administration.
- Outpatient diaries for recording daily selpercatinib dosing, H2 blockers and antacids.
- AEs.
- Concomitant medications.
- Patient-reported outcomes to be completed pre-dose:
    - For MTC patients with diarrhea present at baseline: bowel diary.
    - European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30).

Day 8

- Symptom-directed physical examination, weight, and ECOG.
- Vital signs: pre-dose (up to 4 hours pre-dose, as close to dosing as possible is preferred) and 2 hours post-dose (±30 minutes). Vital signs should be performed prior to collection of PK blood sample drawn at that time point.
- Resting 12-lead ECG: perform a single ECG at 2 hours (± 10 minutes) post-selpercatinib dosing. On C1D8 PK collection, an extra ECG should be timed prior to the PK sample being drawn. If any ECG demonstrates QTcF 481-500 msec, perform an additional ECG at the same day, specific time judged by investigator. If any ECG demonstrates QTcF > 500 msec, repeat the ECG twice (triplicate in total) at the same day, specific time judged by investigator, and manually review to confirm accuracy.
- Hematology (as described in Appendix H).
- Serum chemistries (as described in Appendix H).
- Blood sample of intensive PK (2 mL whole blood) for a total 12 subjects: pre-dose, and post-dose at 1, 2 and 4 hours (±15 minutes), and 8 hours (±30 minutes). Exact clock time (24h format) of sample collection and of dose administration should be recorded.
- Outpatient diaries for recording daily selpercatinib dosing, H2 blockers, and antacids.
- AEs.
- Concomitant medications.
- For MTC patients with diarrhea present at baseline: bowel diary.

Day 15

- Symptom-directed physical examination, weight, and ECOG.
- Vital signs: pre-dose (up to 4 hours pre-dose, as close to dosing as possible is preferred).
- Hematology (as described in Appendix H).
- Serum chemistries (as described in Appendix H).
- Thyroid panel, including TSH, FT_3, and FT_4.
- Urinalysis.
- Calcitonin, CEA: for patients with MTC only. For each patient, all tests for calcitonin and CEA should be performed in the same laboratory to minimize intra-patient, lab-to-lab variability in their measurement.
- Thyroglobulin: for patients with non-MTC thyroid cancer only (unless not measurable due to presence of anti-thyroglobulin antibodies). For each patient, all tests for thyroglobulin should be performed in the same laboratory to minimize intra-patient, lab-to-lab variability in their measurement.
- Blood cortisol, ACTH, 24-hour urine for free cortisol: optional for patients with Cushing's disease related to their cancer. If done, urine collection should begin pre-dose.
- Outpatient diaries for recording daily selpercatinib dosing, H2 blockers, and antacids.
- AEs.
- Concomitant medications.

- For MTC patients with diarrhea present at baseline: bowel diary. Two patient bowel diary cards will be dispended on C1D15, another card will be used on C1D22.

Day 22

- Telephone contact for safety.

7.3 Cycles 2 and Higher

The following procedures will be performed prior to dosing as noted. Routine clinic visits performed within ±2 days of the nominal visit day will not be considered protocol deviations.

- Symptom-directed physical examination, weight, and ECOG: Day 1 each cycle starting with C2.
- Vital signs: up to 4 hours pre-dose on Day 1 each cycle starting with C2.
- Resting 12-lead ECG (2 hours [±10 minutes] post-dose on C2D1, C3D1, C4D1, C5D1 and C6D1 and every 12 weeks thereafter). Additional ECGs may be performed if clinically indicated.
- Blood sample of population PK (2 mL whole blood) for all enrolled subjects: each cycle D1 predose.
- Serum or urine pregnancy test for women of childbearing potential (surgically sterilized females or those who have not experienced menses for at least 2 years are not required to be tested): Day 1 each cycle starting with C2.
- Hematology: (as described in Section 7.1).Day 1 each cycle starting with C2.

  Note: Patients found to have treatment-emergent hematologic toxicity of Grades 3 or 4 will be monitored at least weekly until resolution.
- Serum chemistries (as described in Appendix H): Day 1 each cycle starting with C2.

  Note: Patients found to have treatment-emergent laboratory toxicity of Grades 3 or 4 will be monitored at least weekly until resolution.
- LFTs, including AST, ALT, ALP, and total and direct bilirubin: C2D15 and C3D15.
- Thyroid panel: Day 1 of odd-numbered cycles, starting with C3.
- Urinalysis: D1 C2, and as clinically indicated.
- Dispense selpercatinib.
- Selpercatinib administration.
- Outpatient diaries for recording daily selpercatinib dosing, H2 blockers and antacids.
- AEs.
- Concomitant medications.
- Patient-reported outcomes:
  - For MTC patients with diarrhea present at baseline: bowel diary, Day 1 each cycle starting with C2.
  - EORTC QLQ-C30, completed at the same cycle visits as disease assessments until EOT.

The following procedures will be performed as planned even if cycles are delayed. As a result, the following procedures may not always occur at the beginning of a cycle.

- Calcitonin, CEA: for patients with MTC only; Day 1 of C2 and odd-numbered cycles, starting with C3 through C13, and every 12 weeks thereafter (±7 days of each radiologic disease assessment). For each patient, all tests for calcitonin and CEA should performed in the same laboratory to minimize intra-patient, lab-to-lab variability in their measurement.
- Thyroglobulin: for patients with non-MTC thyroid cancer only, unless not measurable due to presence of anti-thyroglobulin antibodies): Day 1 of C2 and odd-numbered cycles, starting with C3 through C13, and every 12 weeks thereafter (±7 days of each radiologic disease assessment). For each patient, all tests for thyroglobulin should be performed in the same laboratory to minimize intra-patient, lab-to-lab variability in their measurement.
- Blood cortisol, ACTH, 24-hour urine for free cortisol: for patients with Cushing's disease related to their cancer. Day 1 of C2 and odd-numbered cycles, starting with C3 through C13, and every 12 weeks thereafter (±7 days of each radiologic disease assessment). If done, urine collection should begin pre-dose.
- Radiographic disease assessment: every 8 weeks (±7 days) beginning with C3D1 through C13D1, and every 12 weeks (±7 days) thereafter until PD, withdrawal of consent, or initiation of a new anticancer therapy(ies), including imaging of the chest, abdomen, and pelvis, utilizing the same modality(ies) as used for the baseline imaging assessment. Additionally, any studies performed at baseline that are positive for sites of disease should be repeated at all post baseline assessments. Additional studies can also be performed as clinically indicated. Please refer to the Imaging Manual for guidelines on how the various imaging studies should be performed.
  Notes:
  - Patients who discontinue study drug for reasons other than PD (e.g., AE, noncompliance, etc.) may (but, for practical reasons and to minimize patient inconvenience, are not required to) have scans performed and collected as defined above.
  - Post-baseline imaging of the brain using the same modality as at baseline should be performed for patients with evidence of CNS disease at baseline and if clinically indicated.
  - If consistent with local regulatory guidelines, an initial post-baseline assessment after 4 weeks of treatment (±7 days) is encouraged**.** If this scan is performed, the next scan should continue according to the schedule above (beginning at C3D1).
  - If consistent with local regulatory guidelines, confirmatory imaging a minimum of 4 weeks (e.g., 28 days) after the first imaging studies that demonstrate a tumor CR or PR by RECIST 1.1 is encouraged. If this scan is performed, the next scan should continue according to the schedule above.

7.4 End of Treatment Visit (All Patients)

Within 7 days of last dose of study drug or at the time of premature discontinuation of treatment, the following procedures will be performed at the EOT visit:

- Scheduling of tumor tissue biopsy from patients who experience PD (optional and if it can be safely performed in the judgement of the Investigator).
- Symptom-directed physical examination, weight, and ECOG.
- Vital signs.
- Resting 12-lead ECG.
- Hematology.
- Serum chemistries.
- Urinalysis.
- Calcitonin, CEA: for patients with MTC only. For each patient, these should be performed in the same laboratory as prior testing to minimize intra-patient variability in measurement.
- Thyroglobulin: for patients with non-MTC thyroid cancer only (unless not measurable due to presence of anti-thyroglobulin antibodies). For each patient, all tests for thyroglobulin should be performed in the same laboratory to minimize intra-patient, lab-to-lab variability in their measurement.
- Blood cortisol, ACTH, 24-hour urine for free cortisol: optional for patients with Cushing's disease related to their cancer.
- Radiographic disease assessment (if not performed within the last 2 cycles). Patients who have an ongoing CR or PR and discontinue study drug for reasons other than PD (e.g., AE, noncompliance, etc.), may (but, for practical reasons and to minimize patient inconvenience, are not required to) have scans collected ~ every 8-12 weeks as outlined above until documented PD.
- Return unused selpercatinib.
- Outpatient diaries for recording daily selpercatinib dosing, H2 blockers, and antacids.
- AEs.
- Concomitant medication(s).
- Patient-reported outcomes:
    - For MTC patients with diarrhea present at baseline: bowel diary.
    - EORTC QLQ-C30.

7.5 Safety Follow-up Visit (SFU)

Twenty-eight (28) days (+7 days) after the final dose of study drug (may be performed as part of the EOT visit if the latter was performed at least 28 days after final dose of the last cycle), the following will be performed:

- Symptom-directed physical examination, weight, and ECOG.

- Vital signs.
- Resting 12-lead ECG: only if prior ECG reading showed treatment-emergent abnormalities.
- Hematology.
- Serum chemistries.
- Urinalysis.
- Status of unresolved SAEs (if unresolved SAEs exist at the time of this visit, subsequent assessment for resolution may be conducted by phone if patient is not able to return to clinic).
- AEs.
- Concomitant medications.

7.6 Long-term Follow-up (LTFU)

After treatment discontinuation, for patients who remain on study, LTFU will occur approximately every 3 months (±1 month), until the patient has withdrawn consent for further participation, is lost to follow-up, has died or the Sponsor makes a decision to close the study. Assessments may include: subsequent anticancer therapy(ies) and survival status. Long-term follow up may be conducted by phone. For any patient who is lost to follow-up, the study site will attempt to ascertain survival information via public database search. If survival status still cannot be ascertained, patients will be considered lost to follow-up and will be censored appropriately.

If a patient discontinues study treatment for reasons other than PD, withdrawal of consent, lost to follow-up or initiation of a new anticancer therapy(ies), the patient may (but, for practical reasons and to minimize patient inconvenience, is not required to) undergo disease assessment by imaging as specified in Section 7.3 until PD, withdrawal of consent, lost to follow-up or initiation of a new anticancer therapy(ies) utilizing the same modality(ies) used for the baseline imaging assessment.

7.7 Procedures for Special Tests

7.7.1 Tumor Measurements

Tumors will be assessed by the Investigator according to the guidelines provided in Section 7 and the Imaging Manual. Investigators should use the same method consistently for an individual patient throughout the study. Assessments of both measurable and non-measurable disease will be made by the Investigator using RECIST 1.1 (refer to Appendix G); as appropriate to tumor type; or a comparable assessment method depending on location of tumor.

7.7.2 Central Collection of Radiographic Studies

Baseline screening radiographic studies and all subsequent radiographic studies (including any unscheduled scans performed for any clinical reasons) and their associated reports will be collected and stored for future independent radiological review.

7.7.3 Pharmacokinetics

Plasma samples will be obtained for patients as outlined in SoA. Additional PK assessments may be conducted in patients when considered necessary by the Investigator to understand exposure in relationship to possible safety or efficacy findings or if there is a change to the formulation of selpercatinib administered. Samples will be collected and handled as outlined in the Laboratory Manual, and concentrations of selpercatinib will be determined with a validated bioanalytical method. These data will be used to determine parameters such as AUC_{0-t} and plasma terminal elimination half-life ($T_{1/2}$). The 0-8-hour duration of sample collection will be sufficient to cover a significant fraction of the area under the plasma concentration versus time curve.

Serial blood samples for intensive PK monitoring will be collected on C1D1 and C1D8 for a total of 12 patients, blood samples for PopPK will be collected for all enrolled patients. PK parameters calculated from the drug concentrations in these samples will be used to compare the area under the concentration versus time curve from time 0 to infinity ($AUC_{0-\infty}$) on D1 with the area under the concentration versus time curve calculated during the dosing interval at steady state (AUC_{tau}) and detect any auto-inhibition or auto-induction of the pharmacokinetics of selpercatinib (none is expected). Exploratory analyses to determine the presence and structures of metabolites of selpercatinib may also be conducted and the results of these analyses, if conducted, will be reported separately by the Sponsor.

7.7.4 Collection of EORTC QLQ-C30 and Bowel Diary

Paper Quality of Life (QoL) instruments will be administered pre-dose on C1D1.

The EORTC QLQ-C30 and a bowel diary (for MTC patients only) will be used (refer to Appendix J) and should be implemented for newly enrolled patients. Only patients who have completed the questionnaire at baseline should complete subsequent questionnaires at the specified follow-up periods.

For EORTC QLQ-C30, subsequent assessments will occur at the same cycle visits as disease assessments until EOT. Each assessment should be performed before the subject learns the results of his or her restaging.

For MTC patients, the bowel diary assessments will be collected weekly on Cycle 1, and on Day 1 of every cycle thereafter through EOT. Inaccurate recording will not be considered a protocol violation.

7.7.5 Correlative Studies

7.7.5.1 Tumor Samples

Archived tumor samples prior to treatment with selpercatinib are required if available for participation in the trial. Tissue blocks are preferred, otherwise ~10 × 5µm unstained slides should be provided. If sufficient quantity or quality of tissue cannot be provided, patients can undergo a fresh tumor biopsy, if it is considered safe to perform, prior to treatment (refer to Section 7.7.5.2). If patients cannot provide sufficient tumor tissue sample, patients still can be enrolled after discussion between sponsor and investigator and get sponsor's approval. The samples will be used for identification or confirmation of molecular abnormalities in *RET* gene. Samples (including tumor sample and derivatives such as DNA and RNA) will be retained at a facility selected by Lilly for a maximum of 4 years after the last patient visit for the study, or for a shorter period if local regulations and/or ethical review boards (ERBs)/investigational review boards (IRBs) impose shorter time limits. This retention period enables response to regulatory questions related to selpercatinib, after which they will be destroyed.

The sample collection must be captured on the appropriate eCRF and requisition page(s). Refer to the Laboratory Manual for detailed sample collection, storage, and shipment information.

7.7.5.2 Fresh Tumor Biopsies

Fresh tumor samples will be used for identification or confirmation of molecular abnormalities in RET and other genes. Fresh tumor biopsies are strongly encouraged when the Investigator feels it is appropriate and safe to do so.

Prior to Selpercatinib Treatment

Required: A fresh tumor biopsy must be obtained prior to selpercatinib for all patients who do not have archival tumor tissue available (or who have insufficient tissue quantity or quality—refer to Section 7.7.5.1) and for whom, in the opinion of the Investigator, a fresh tumor biopsy can be safely performed.

Optional: If archived tumor tissue was obtained prior to progression on the last MKI with anti-RET activity, a fresh biopsy of a lesion may be obtained if the patient provides informed consent and it can be safely performed. The purpose of the fresh tumor biopsy is to identify genetic alterations related to progression after the previous MKI(s).

8 Study Assessments and Procedures

Table 7-1 provides the Schedule of Activities for this study.

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, scans, RET testing) 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.

8.1 Efficacy Assessments

8.1.1 Imaging

To evaluate PFS, tumor assessments will be performed for each patient at the times shown in the Schedule of Activities (Table 7-1) or whenever clinically indicated. Radiologic assessments obtained previously as part of routine clinical care may be used as baseline assessment provided they are of diagnostic quality and were done no more than 28 days before the first dose of study drug.

Computed tomography (CT) scans, including spiral CT, are the preferred methods of measurement (CT scan thickness recommended to be £5 mm); however, magnetic resonance imaging (MRI) is also acceptable in certain situations, such as when body scans are indicated or if there is a concern

about radiation exposure associated with CT. Intravenous and oral contrast is required unless medically contraindicated.

The CT portion of a positron emission tomography (PET)-CT scan may be used as a method of response assessment if the site can document that the CT is of identical diagnostic quality to a diagnostic CT (with intravenous and oral contrast). A PET scan alone or as part of a PET-CT may be performed for additional analyses but cannot be used to assess response according to RECIST 1.1 (Eisenhauer et al. 2009).

The method of tumor assessment used at baseline must be used consistently throughout the study. Radiologic scan of the thorax, abdomen, and pelvis is required, as well as any other areas with suspected disease involvement. A baseline intracranial evaluation with CT or MRI is required for patients with known CNS lesions. A baseline bone scintigraphy (preferred) or PET scan or PET component of PET/CT scan is required for patients with known nonmeasurable bone lesions (include new confirmed lesions in screen period). It is allowed to skip bone scintigraphy or PET scan or PET component of PET/CT scan at subsequent tumor assessments, under the circumstance where other imaging methods cover the bone lesion(s). Otherwise, bone scintigraphy or PET scan or PET component of PET/CT scan may be obtained every 24 weeks (±7 days) or more often if clinically indicated. Please see the Site Imaging Manual for guidelines on how the various imaging studies should be performed and transmitted for central review.

8.2 Safety Assessments

8.2.1 Electrocardiograms

ECG monitoring should be performed as outlined in the SoA (Table 7-1). The actions below should be taken if the triplicate average QTcF is greater than 500 msec.

- Manually review to confirm accuracy
- Assess for alternative causes (concomitant medications, electrolyte abnormalities, presence of pacemaker). Potassium should be ≥4 mEq/L and <ULN and magnesium and calcium should be within normal limits.
- Institutional guidelines or SOC measures for management of QTcF interval >500 msec and/or associated arrhythmias should be initiated.
- Clinical chemistry should be assessed and if electrolytes are abnormal, they should be repeated as indicated.

If a patient experiences a QTcF interval >500 msec and if the investigator deems it in the best interest of the patient, the patient may continue treatment with study drug (with a dose reduction).

8.2.2 Clinical Safety Laboratory Assessments

- Investigator sites may use local laboratories to determine patient eligibility and treatment decisions.
- In addition, blood will be collected,
  - See Appendix H for the list of clinical laboratory tests to be performed and Table 7-1 (Schedule of Activities) for the timing and frequency.
  - The investigator should review any clinically significant abnormal laboratory findings and assess relevance to patient care. If the laboratory findings are clinically significant, the investigator should document the findings as an adverse event in the case report form. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are based on investigator judgement.
- Regardless of whether or not central or local laboratory tests are used to determine patient care decisions, all laboratory tests with values considered clinically significantly abnormal during participation in the study or until completion of SFU should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator.
  - 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 H, must be conducted in accordance with the laboratory manual and the SoA.

8.2.2.1 Hepatic Safety Monitoring

If a study participant enrolled with baseline ALT/AST <1.5X ULN experiences elevated ALT/AST ≥3X ULN and elevated total bilirubin level (TBL) ≥2X ULN, or ALT/AST ≥5X ULN, LFTs (AST, ALT, ALP and total and direct bilirubin) 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 should be initiated by the investigator and in consultation with the study CRP/CRS. Monitoring of LFTs should continue until levels normalize or return to approximate baseline levels.

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, LFTs 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 LFTs should continue until levels normalize or return to approximate baseline levels.

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

- In patients enrolled with baseline ALT/AST (<1.5 ULN) the threshold for close monitoring is as follows:
    a. Elevated ALT/AST ≥3X ULN and elevated TBL ≥2X ULN
    b. ALT/AST ≥5X ULN on 2 consecutive tests
- In patients enrolled with elevated baseline ALT/AST (≥1.5X ULN) (regardless of whether or not they have hepatic metastasis) the threshold for close monitoring is:
    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

8.2.3 Adverse Events and Serious Adverse Events

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 informed consent form (ICF) is signed, study site personnel will record via case report form (CRF) the occurrence and nature of each participant's preexisting 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. 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 Directory for Regulatory Activities (MedDRA) Lower level term (LLT) dictionary. The investigator will use CTCAE v5.0 to assign AE severity grades.

Investigators should record their assessment of the potential relatedness of each AE to protocol procedure or 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, 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, and/or study procedure and the AE. The investigator answers yes/no when making this assessment.

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.

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 8.2.3.1) if it is considered reasonably possibly related to study procedure.

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 (see Section 8.2.2.1).

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.

Suspected Unexpected Serious Adverse Reactions (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.

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, to monitor quality, and to facilitate process and product improvements.

Patients 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.

8.2.3.1 Time Period and Frequency for Collecting AE and SAE Information

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

AEs that begin before the start of study intervention but after obtaining informed consent will be recorded on the AE CRF, not the Medical History CRF.

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

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

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

8.2.3.2 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 SoA).

8.2.3.3 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 comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.
- Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- 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.

8.2.3.4 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 SFU.
- 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 I.
- 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 I.
- 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.

8.2.3.5 Cardiovascular and Death Events

Not applicable.

8.3 Treatment of Overdose

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

8.4 Pharmacokinetics

At the visits and times specified in the Schedule of Activities (Table 7-1), blood samples of approximately 2 mL each will be collected to determine the plasma concentrations of selpercatinib.

A maximum of 6 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.

For 12 subjects in intensive PK testing, PK test performed on C1D1: Up to pre-dose, and post-dose 1 hour (±15 minutes), 2 hours (±15 minutes) , and 4 hours (±15 minutes),8 hours (±30 minutes) and 12 hours (±30 minutes), C1D8: Up to pre-dose, and post-dose 1 hour (±15 minutes), 2 hours (±15 minutes), and 4 hours (±15 minutes) and 8 hours (±30 minutes). For all enrolled subjects in PopPK testing, PK test performed on each cycle D1. Exact clock time (24h format) of sample collection and of dose administration should be recorded. Time of previous 3 doses should also be recorded.

Additional PK may also be assessed in patients when considered necessary by the Investigator to understand exposure in relationship to possible safety.

PK samples will be retained at a facility selected by Lilly for a maximum of 4 years after the last patient visit for the study.

8.5 Pharmacodynamics

Not applicable.

8.6 Biomarker

Biomarker research is performed to address questions of relevance to drug disposition, target engagement, 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 deoxyribonucleic acid (DNA), ribonucleic acid (RNA).

Tissue samples for biomarker research will be collected at the times specified in the Schedule of Activities (Section 1.3) where local regulations allow. 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 addition, for all patients, an anonymized/redacted Molecular Pathology Report or other report(s) describing tumor *RET* (and other) alteration analysis should be submitted to the Sponsor, designee, or central laboratory.

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.

Archived tumor tissue should be submitted for Cohort 1 and 2, either via tumor block (preferred) or ~10 × 5µm unstained slides. We may have extracted DNA and RNA that be obtained from the tissue samples for central lab *RET* eligibility testing or *RET* alteration confirmation. Lilly has a right to retain a portion of the submitted tissue. Archival blocks will be sectioned and returned to the study site or patients. Slides and tissue samples collected on-study will not be returned. If patients cannot provide sufficient tumor tissue sample, patients still can be enrolled after discussion between sponsor and investigator and get sponsor's approval. Patients who do not have sufficient archival tumor tissue available may undergo a fresh tumor biopsy, if it is considered safe to perform, prior to treatment.

Samples (including tumor sample and derivatives such as DNA and RNA) will be retained at a facility selected by Lilly for a maximum of 4 years after the last patient visit for the study, or for a shorter period if local regulations and ERBs impose shorter time limits. This retention period enables response to regulatory questions related to selpercatinib.

8.7 Medical Resource Utilization and Health Economics

Patient-reported questionnaires will be collected via a paper source document according to the Schedule of Activities

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)

Bowel Diary (for MTC patients only)

Bowel Diary adapted and modified from patient-reported questionnaire (STIDAT) by Michelle Lui et al., Development and validation of a patient-reported questionnaire assessing systemic therapy induced diarrhea in oncology patients, HEALTH AND QUALITY OF LIFE OUTCOMES 15:249 (2017).

9 Statistical Considerations

A full Statistical Analysis Plan (SAP) will provide specific details on the analytical methods and data displays.

9.1 Study Endpoints

9.1.1 Primary Endpoint

- ORR using RECIST v1.1 as assessed by independent review committee (IRC).

9.1.2 Secondary Endpoints

- Parameters of anti-tumor activity/clinical benefit, including: ORR (by Investigator), DOR (by IRC and Investigator), CNS ORR (by IRC), CNS DOR (by IRC), time to any and best response (by IRC and Investigator), CBR (by IRC and Investigator), PFS (by IRC and Investigator), and OS
- Frequency, severity, and relatedness of TEAEs and SAEs, changes in hematology and blood chemistry values, and assessments of physical examinations, vital signs, and ECGs
- Plasma concentrations of selpercatinib and PK parameters, including, but not limited to, $AUC_{0\text{-}24}$, C_{max}, and T_{max}

9.1.3 Exploratory Endpoints

- Differences in efficacy and safety based on selpercatinib PK parameters
- Changes in CEA and calcitonin (patients with MTC), thyroglobulin (non-MTC thyroid cancer patients), and ACTH and cortisol (patients with Cushing's disease related to their cancer) with selpercatinib treatment
- Changes from baseline in disease-related symptoms and HRQoL, as measured by EORTC QLQ-C30, and patient bowel diaries (MTC patients only)
- Time from PD_1 to PD_2 for patients who continue to receive study treatment beyond disease progression

9.2 Analysis Populations

Enrolled population: will include all enrolled patients.

Treated population will include all enrolled patients who received at least one dose of selpercatinib. This population will be used for safety analysis and efficacy analysis other than primary efficacy analysis.

Primary efficacy analysis population: will include all treated patients enrolled in Cohort 1 and 2 who have confirmed RET fusion positive solid tumor or RET mutant MTC by central lab, respectively. The primary efficacy analysis will be conducted on this population.

Pharmacokinetic population will include all treated patients with baseline and at least one postbaseline evaluable PK sample.

9.3 Determination of Sample Size

For Cohort 1-2, at least 20 patients will be targeted for enrollment in each cohort. The main objective is to provide for a preliminary assessment of the antitumor activity of selpercatinib in Chinese patients with RET alterations. Table 9-1 presents the lower bounds of 2-sided exact 95% confidence intervals based on different choice of sample size and observed ORR. If the observed ORR is high (i.e., exceeds 45%) within a cohort of 20 patients, then the corresponding lower limit of a 2-sided exact 95% confidence interval will exclude true response rates that are considered marginal or uninteresting.

Up to 25 patients will be enrolled into Cohort 3 based on clinical considerations.

In addition, with an overall sample size of 75, the probability of observing one or more instances of a specific AE with a true incidence rate of 2% and 5% is approximately 80% and 98%, respectively.

Table 9-1 Lower bounds of 2-sided exact 95% confidence intervals based on different sample size and observed ORR

n \ ORR	0.4	0.45	0.5	0.55	0.6	0.65
10	0.12	0.15	0.19	0.22	0.26	0.3
20	0.19	0.23	0.27	0.32	0.36	0.41
25	0.21	0.25	0.30	0.34	0.39	0.44
30	0.23	0.27	0.31	0.36	0.41	0.46
40	0.25	0.29	0.34	0.38	0.43	0.48
50	0.26	0.31	0.36	0.40	0.45	0.50
60	0.28	0.32	0.37	0.42	0.47	0.52

9.4 Statistical Methods

9.4.1 Demographics and Baseline Characteristics

Descriptive summaries of demographic and baseline characteristics for all enrolled patients will be tabulated. Patients will be tabulated by cohort and overall.

9.4.2 Safety Analyses

Safety will be assessed by clinical review of all relevant parameters including AEs, SAEs, laboratory values, vital signs, ECG results, concomitant medications, and thyroid function. Unless specified otherwise, the safety analyses will be conducted for the safety population defined in Section 8.2 from all cohorts. Tabulations will be provided by cohort and overall.

Summary tables and listings will be provided for all reported TEAEs, defined as AEs that start on or after the first administration of study drug. The reported AE term will be assigned standardized coding using MedDRA; the MedDRA version shall be specified in study documents.

TEAEs will be summarized based on the number and percentage of patients experiencing the event by MedDRA System Organ Class (SOC) and preferred term (PT). The causal relationship between the occurrence of an AE and study drug will be judged by the Investigator based on the conventions described in Section 8.2. In the event a patient experiences repeat episodes of the same AE, then the event with the highest severity grade and strongest causal relationship to study drug will be used for purposes of incidence tabulations.

Tabular summaries will be provided for:

- All TEAEs.
- TEAEs by relationship (yes, no) to underlying disease, other medical conditions or concomitant medications, and maximum severity grade.
- TEAEs with action of study drug delayed/interrupted or treatment reduced.
- TEAEs with action of study drug discontinued.
- All SAEs.
- SAEs by relationship (yes, no) to underlying disease, other medical conditions, or concomitant medications.

All deaths including on-study death that occur within 28 days of treatment discontinuation will be reported in a patient listing, which will include the primary cause of death and the number of days

between the date of the last dose of study drug and death. A summary of the anticancer therapies received after discontinuation of study drug will be provided.

Hematology and serum chemistries will be summarized in a descriptive manner by calculating the mean, standard deviation, median, and range.

9.4.3 Efficacy Analyses

The efficacy analyses will be conducted on the efficacy population unless otherwise specified.

Tumor response will be assessed using RECIST 1.1 (Table 11-8). The objective response rate (ORR) is defined as the number of patients who achieve a best overall response of complete response (CR) or partial response (PR) that are confirmed divided by the total number of efficacy analysis population. ORR, accompanied by 2-sided 95% exact binomial CIs, will be summarized. The analysis of ORR will be conducted both by the responses determined by IRC and investigator.

Waterfall plots will be used to depict graphically the maximum decrease from baseline in the sum diameters of target lesions.

DOR will be calculated for patients who achieve CR or PR. For such patients, DOR is defined as the number of months from the start date of CR or PR (whichever response status is observed first) and subsequently confirmed, to the first date that PD is objectively documented. If a patient dies, irrespective of cause, without documentation of PD beforehand, then the patient's date of death will be used to denote the response end date.

PFS will be derived for each patient as the number of months from the date of the first dose of study drug to the earlier of documented PD or death due to any cause. Patients who are alive and without documented PD as of a data analysis cutoff date will be right-censored.

OS will be derived for each patient as the number of months from the date of the first dose of study drug to the date of death, irrespective of cause. Patients who are alive or lost to follow-up as of a data analysis cutoff date will be right-censored. The censoring date will be determined from the last date the patient was known to be alive or data analysis cutoff date, whichever occurs first.

The detailed censoring rule for lifetime data such as DOR, PFS and OS will be specified in SAP. DOR, PFS, and OS will be summarized descriptively using the Kaplan-Meier method with 95%

CIs. Median follow-up for each endpoint will be estimated according to the Kaplan-Meier estimate of potential follow-up (Schemper and Smith 1996).

Analyses of other secondary and exploratory endpoints will be provided in the SAP.

9.4.4 Pharmacokinetic Analyses

Plasma concentrations of selpercatinib will be determined with a validated bioanalytical assay. The following PK parameters will be calculated from plasma concentrations determined on C1D8: C_{max}, T_{max}, area under the concentration versus time curve from time 0 to t ($AUC_{0–t}$), $AUC_{0–\infty}$, apparent oral clearance (CL/F), apparent volume of distribution (V_z/F), and $T_{1/2}$.

Summary statistics will be generated by cohorts as appropriate.

9.4.5 Interim Analyses and Data Monitoring

An interim analysis is planned to trigger early interaction with regulatory authorities. The data cutoff date is determined such that approximately half of enrolled patients will have received at least one post-baseline tumor assessment.

The primary analysis will be performed after all enrolled patients have been followed up for a sufficient amount of time, defined as with at least two post-baseline tumor assessments. The primary analysis may be updated upon request from regulatory authorities.

10 Study Administration

10.1 Regulatory and Ethical Considerations

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

- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (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

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.

10.2 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 enrolled 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.

10.3 Data Management

10.3.1 Data Protection

- Participants will be assigned a unique identifier by the investigator. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.3.2 Committees Structure

The primary endpoint ORR will be assessed by IRC. Independent central review will consist of independent radiologists to perform response assessments and determination of disease progression per RECIST 1.1.

10.3.3 Dissemination of Clinical Study Data

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

10.3.4 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.

10.3.5 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, clinical outcome assessment (COA) data (questionnaires) will be collected by the subject, via a paper source document and will be transcribed by the investigator site personnel into the EDC system.

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 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.

10.3.6 Source Documents

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

10.4 Study Monitoring

Prior to the start of the study, the Sponsor's monitor will contact the clinical site to discuss the protocol and data collection procedures and conduct applicable training of site personnel. The Sponsor and its designees will also periodically contact the clinical site during the conduct of the study (which will include on-site visits) in accordance with applicable regulations and GCP. During these contacts, the monitoring activities will include:

- Checking and assessing the progress of the study.
- Reviewing study data collected to date for completeness and accuracy.
- Conducting source document verifications by reviewing each patient's eCRF against source documents.
- Identifying any issues and addressing resolutions.
- Recording and reporting protocol deviations not previously reported to the Sponsor.
- Confirming that SAEs have been properly reported to the Sponsor and submitted to the IRB/IEC if appropriate.

These activities will be done in order to verify that the data are authentic, accurate, and complete; that the safety and rights of the patient are being protected; and that the study is conducted in accordance with the currently approved protocol, ICH GCP, and all applicable regulatory requirements. Additionally, to ensure compliance with ICH GCP and all applicable regulatory requirements, the Sponsor or designee may conduct a quality assurance audit.

10.5 Termination

Upon completion of the study, the following activities, when applicable, must be conducted by the site monitor and the Investigator:

- Submission of all study data to the Sponsor.
- Completion of all data clarifications and/or resolutions.
- Reconciliation and final disposition of investigational product.
- Review of site study files for completeness.
- In addition, the Sponsor reserves the right to temporarily suspend or prematurely terminate this study for any reason.

If the study is suspended or terminated for safety reasons, the Sponsor will promptly inform the Investigator and will also inform the IRB/IEC with the reasons for the action. In the event of prematurely termination, all study data must be submitted to the Sponsor. In addition, the clinical site must document final disposition of all unused investigational product in accordance with the Sponsor's procedures.

10.6 Records Retention

Patient records, source documents, monitoring visit logs, investigational product inventory, regulatory documents, and other correspondence pertaining to the study must be maintained in the appropriate site study files according to ICH GCP and applicable regulatory requirement(s). These records will be retained for the period required by the institution or site policy. Prior to transfer or destruction of these records, the Sponsor must be notified in writing.

10.7 Confidentiality of Information

Patient names will remain confidential and will not be supplied to the Sponsor or its designee. The Investigator will maintain a personal patient identification list (patient and treatment numbers with the corresponding patient names) to enable records to be identified.

11 Appendices

Appendix A Examples of Multikinase Inhibitors (MKIs) with Anti-RET Activity

Table 11-1 Examples of Multikinase Inhibitors (MKIs) with Anti-RET Activity

Multikinase Inhibitors
Cabozantinib
Vandetanib
Alectinib
Lenvatinib
Ponatinib
Regorafenib
Sunitinib
Sorafenib
Motesanib
sitravatinib (MGCD516)
Anlotinib
Apatinib

Appendix B Examples of *RET* Activating Mutations

Table 11-2 Examples of *RET* Activating Mutations

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, Y791F/N
14	V804L, V804M, Y806C, E818K, 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.

References: (Dvorakova, Vaclavikova et al. 2008, Agrawal, Jiao et al. 2013, Krampitz and Norton 2014, Ji, Oh et al. 2015, Wells, Asa et al. 2015, Heilmann, Subbiah et al. 2016, Romei, Casella et al. 2016, Kato, Subbiah et al. 2017).

Appendix C Examples of Validated Oncogenic Drivers

Table 11-3 provides examples of oncogenic drivers that may cause resistance to selpercatinib.

Table 11-3 Examples of Validated Oncogenic Drivers

Tumor Type	**Oncogenic Driver(s)**
NSCLC	Targetable mutation in *EGFR* or *MET,* targetable rearrangement involving *ALK* or *ROS1*, or activating mutation in *KRAS*
Thyroid (non-MTC)	Targetable mutation in *BRAF* or activating mutation in *RAS* genes
MTC	Targetable rearrangement involving *ALK* or activating mutation in *RAS* genes
Pancreatic	Activating mutation in *KRAS*
Colorectal	Targetable mutation in *BRAF* or *PIK3CA* or activating mutation in *RAS* genes
Breast	Targetable mutation in *PIK3CA* or alteration in *HER2*
Other	Targetable mutation/rearrangement known to occur in the specific disease type

Abbreviations: MTC = medullary thyroid cancer. NSCLC = non-small cell lung cancer.

Appendix D Inhibitors and Inducers of CYP3A4

Note: Avoid concomitant use of strong and moderate CYP3A inhibitors or inducers with selpercatinib. If concomitant use of strong and moderate CYP3A inhibitors cannot be avoided, reduce the selpercatinib dosage and monitor the QT interval with ECGs more frequently.

Table 11-4 Examples of Inhibitors of CYP3A4

Strong inhibitors [a]	**Moderate inhibitors** [b]
Boceprevir	amprenavir
Clarithromycin	aprepitant
Conivaptan	atazanavir
grapefruit juice	ciprofloxacin
Indinavir	darunavir
Itraconazole	diltiazem
Ketoconazole	erythromycin
Lopinavir	fluconazole
Mibefradil	fosamprenavir
Nefazodone	imatinib
Nelfinavir	verapamil
Posaconazole	
Ritonavir	
saquinavir	
telaprevir	
telithromycin	
voriconazole	

Abbreviations: CYP3A4 = cytochrome P450 3A4.
[a] Increases the area under the curve (AUC) of the substrate by ≥ 5-fold.
[b] Increases the AUC of the substrate by 2- to 5-fold.

Table 11-5 Examples of Inducers of CYP3A4

Strong inducers [a]	**Moderate inducers** [b]
avasimibe	Bosentan
carbamazepine	Efavirenz
enzalutamide	Etravirine
phenytoin	Modafinil
rifampin	Nafcillin
St John's wort	

Abbreviations: CYP3A4 = cytochrome P450 3A4.

[a] Increases the area under the curve (AUC) of the substrate by ≥ 5-fold.

[b] Increases the AUC of the substrate by 2- to 5-fold.

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

http://www.jp-orangebook.gr.jp/cgi-bin/search/search_e.cgi.

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 www.crediblemedicines.com for a current list of agents known to cause QTc prolongation as well as agents with a possible or conditional risk.

Appendix E Proton Pump Inhibitors (PPIs)

Patients should avoid concomitant use of a PPI with selpercatinib. If concomitant use cannot be avoided, take selpercatinib with food when coadministered with a PPI.

Table 11-6 Examples of Proton Pump Inhibitors (PPIs)

omeprazole (Omepral®)
esomeprazole (Nexium®)
lansoprazole (Takepron®)
pantoprazole (Protonix®)
rabeprazole (Pariet®)
dexlansoprazole (Dexilant®)

Abbreviations: PPI = proton pump inhibitor

Appendix F Performance Scales

Table 11-7 Eastern Cooperative Oncology Group (ECOG) Performance Scale

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work
2	Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Appendix G Tumor Measurements and Assessment of Disease Response using RECIST version 1.1

Tumor measurements are to be performed for all patients during Screening, as follows (as summarized in Section 7.1):

Baseline disease assessment: radiographic tumor measurements using CT) or MRI of chest, abdomen, and pelvis, and any other areas with suspected disease involvement, and CT or MRI of brain within 28 days of C1D1. For brain imaging, MRI without and with contrast is preferred, CT without and with contrast is acceptable if MRI is medically contraindicated. For each modality, IV and oral contrast should be utilized where applicable unless medically contraindicated. If CT/PET is utilized, the CT component of CT/PET must be of the same quality as a dedicated diagnostic CT scan, i.e., with IV and oral contrast, and 5 mm or less slice thickness.

Notes:

- In patients with thyroid and other head and neck cancers, imaging of the relevant areas (e.g., neck, skull base) is required at baseline; other areas of scanning may differ depending on disease type. Refer to the Imaging Manual for details.
- Additional scans can be performed as needed to evaluate potential sites of disease.
- Disease assessments will utilize RECIST 1.1 as appropriate to tumor type (refer to Section 7.7.1).
- Guidelines on the technical parameters of how scans should be performed will be provided in a separate Imaging Manual that will be distributed to the sites.

Thereafter, tumor measurements and disease response assessments are to be performed as follows (as summarized in Section 7.3):

Radiographic disease assessment: every 8 weeks (±7 days) beginning with Cycle 3 Day 1 through Cycle 13 Day 1 and every 12 weeks (±7 days) (thereafter until PD, withdrawal of consent, or initiation of a new anticancer therapy(ies), including imaging, of the chest, abdomen, and pelvis, utilizing the same modality(ies) as used for the baseline imaging assessment. Additionally, any studies performed at baseline that are positive for sites of disease should be repeated at all post baseline assessments. Additional studies can also be performed as clinically indicated. Please refer to the Site Imaging Manual for guidelines on how the various imaging studies should be performed.

Notes:

- Patients who have an ongoing CR or PR and discontinue study drug for reasons other than PD (e.g., AE, noncompliance, etc.) may (but for practical reasons and to minimize patient inconvenience, are not required to) have scans collected as defined above.
- Post-baseline imaging of the brain using the same modality as at baseline should be performed for patients with evidence of CNS disease at baseline, and if clinically indicated.

- If consistent with local regulatory guidelines, an initial post-baseline assessment after 4 weeks of treatment (±7 days) is encouraged. If this scan is performed, the next scan should continue according to the schedule above (beginning at Cycle 3 Day 1).
- If consistent with local regulatory guidelines, confirmatory imaging a minimum of 4 weeks (e.g., 28 days) after the first imaging studies that demonstrate a tumor CR or PR by RECIST 1.1 as appropriate to tumor type, is encouraged. If this scan is performed, the next scan should continue according to the schedule above.

Such assessments also are to be performed at the EOT visit if they had not been performed within the previous 2 cycles.

Anatomical measurements (summed across target lesions) will be documented during Screening and each subsequent evaluation. When possible, the same qualified physician will interpret results to reduce variability. Radiographic images will be maintained at the study site and sent to a central image collection warehouse. Central reading of some or all of the scans may be performed by a third-party vendor who has expertise in evaluating image data. Test results and Investigator's findings will be filed in the patient's source documents.

During Screening, tumor lesions are to be categorized as measurable versus non-measurable and target versus non-target, as follows.

Measurable versus non-measurable

Measurable: Lesions that could accurately be measured in at least one dimension, the longest diameter in the plane of measurement to be recorded as:

- Tumor lesions: ≥ 10 mm by CT scan
- Malignant lymph nodes: To be considered pathologically enlarged and measurable, the node must be ≥ 15 mm in short axis when assessed by CT scan. At baseline and in follow up, only the short axis will be measured and followed. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

Non-measurable: All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis), and truly non-measurable lesions.

Target versus non-target

Target: All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, are to be identified as target lesions and measured and recorded at Screening. Target lesions are to be selected on the basis of their size (i.e., those with the longest diameter) and suitability for accurate repeated measurement. Lymph nodes may be selected as target lesions; they must be defined as measurable, and only the short axis of the node will contribute to the baseline sum. All

other pathologic nodes with short axis ≥ 10 mm, but < 15 mm should be considered non-target lesions.

Non-target: All other lesions not classified as target lesions (or sites of disease) are to be identified as non-target lesions and are to be recorded in the eCRF. Measurement of non-target lesions is not required.

The sum of the diameters (longest for non-nodal lesions and short axis for nodal lesions) for all target lesions is to be calculated and recorded in the eCRF as the baseline sum diameters.

Disease response in target and non-target lesions will be assessed by the Investigator using RECIST 1.1, according to the categories and criteria described in Table 11-8. The best overall response for each patient will be reported as the best response documented over the sequence of objective statuses recorded using the categories and criteria in Table 11-9.

Table 11-8 Response Evaluation Criteria in Solid Tumors (RECIST version 1.1) Guidelines for Tumor Response

Disease Response Criteria for Target and Non-Target Lesions	
Evaluation of Target Lesions	
Complete Response (CR):	Disappearance of all target lesions. Any pathologic nodes (whether target or non-target lesions) must have a reduction in short axis diameter (SAD) to less than 10 mm.
Partial Response (PR):	At least a 30% decrease in the sum of the diameters (SOD) (LD for non-nodal lesions and SAD for nodal lesions) of target lesions, taking as reference the baseline sum LD.
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.
Progressive Disease (PD):	At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest sum on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5.0 mm. (Note: the appearance of one or more new lesions is also considered progression).
Evaluation of Non-Target Lesions	
Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor marker level.
Incomplete Response/ Stable Disease (SD):	Persistence of one or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits.
Progressive Disease (PD):	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.

Abbreviations: LD = longest diameter.

Source: (Eisenhauer, Therasse et al. 2009). Available at: https://ctep.cancer.gov/protocolDevelopment/docs/recist_guideline.pdf.

Table 11-9 Overall Response Criteria: Time Point Response

Patients with Target and Non-Target Lesions			
Target Lesions	**Non-Target Lesions**	**New Lesions**	**Overall Response**
CR	CR	No	CR
CR	Non-CR / Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not evaluated	Non-PD	No	NE
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD
Patients with Non-Target Lesions Only			
Non-Target Lesions	**New Lesions**	**Overall Response**	
CR	No	CR	
Non-CR / Non-PD	No	Non-CR / Non-PD	
Not all evaluated	No	NE	
Unequivocal PD	Yes or No	PD	
Any	Yes	PD	
Best overall response when confirmation of CR and PR required			
Overall response first time point	**Overall response subsequent time point**	**BEST overall response**	
CR	CR	CR	
CR	PR	SD, PD or PR	
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD	
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD	
CR	NE	SD provided minimum criteria for SD duration met, otherwise, NE	
PR	CR	PR	
PR	PR	PR	
PR	SD	SD	
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD	

PR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
NE	NE	NE

Abbreviations: CR = complete response; NE = inevaluable; PD = progressive disease; PR = partial response; SD = stable disease.

Source: (Eisenhauer, Therasse et al. 2009). Available at: https://ctep.cancer.gov/protocolDevelopment/docs/recist_guideline.pdf.

Appendix H Clinical Laboratory Tests

- All the clinical laboratory testing showed in Appendix H will be performed in local laboratory.
- If there is an abnormal laboratory value or abnormal value for any other diagnostic or screening test (for example, blood pressure increased, neutrophils decreased, etc.) and it is known to be related to a diagnosis (for example, 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.

Clinical Laboratory Tests

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

Coagulation[a]	
PT/INR	PTT/aPTT

Clinical chemistry	
Serum concentrations of:	
Alanine aminotransferase (ALT)	Chloride
Albumin	Creatinine
Alkaline phosphatase	Glucose (random)
Aspartate aminotransferase (AST)	Magnesium
Bilirubin, direct	Potassium
Bilirubin, total	Protein
Blood urea nitrogen (BUN) or blood urea	Sodium
Calcium	

Urinalysis[c]	
Blood	Protein
Glucose	Specific gravity
Ketones	Urine leukocyte esterase[c]
pH	

Pregnancy Test[d]	
Urine pregnancy test	Serum pregnancy test

Thyroid panel[b]	
Free triiodothyronine (FT3)	Thyroid stimulating hormone (TSH)
Free thyroxine (FT4)	

[a] Local or investigator-designated laboratory.

[b] Treatment and enrollment decisions are all based on local laboratory results.
Note: 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 reported on the CRF, unless the CRF specifically provides an entry field for bands.

[c] Urine microscopy may be used in the place of the urine leukocyte esterase assessment to test for the presence of WBCs.

[d] For female patients of childbearing potential.

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CRF = case report form; FT3 = free triiodothyronine; FT4 = free thyroxine; HCT = hematocrit; HGB = hemoglobin; PLT = platelets; PT/INR = prothrombin time/international normalized ratio; PTT = partial thromboplastin time; RBC = red blood cells; TSH = thyroid-stimulating hormone; WBC = white blood cells.

Appendix I 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 1 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's: 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 amenorrhoea 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 selpercatinib.

- 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.

Appendix J European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) and Bowel Diary

EORTC QLQ-C30

The EORTC QLQ-C30 is a questionnaire developed to assess the quality of life of cancer patients. It is a copyrighted instrument, which has been translated and validated in over 100 languages and is used in more than 3,000 studies worldwide. This study is utilizing version 3.0, and the study manual should be consulted for instructions on implementing and scoring.

References:

EORTC website: http://groups.eortc.be/qol/eortc-qlq-c30

Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst. 1993;85(5):365-376 (Aaronson, Ahmedzai et al. 1993).

Bowel Diary

References:

Bowel Diary adapted and modified from patient-reported questionnaire (STIDAT) by Michelle Lui et al., Development and validation of a patient-reported questionnaire assessing systemic therapy induced diarrhea in oncology patients, HEALTH AND QUALITY OF LIFE OUTCOMES 15:249 (2017). Copyright © 2017 Michelle Lui, Daniela Gallo-Hershberg and Carlo DeAngelis (Lui, Gallo-Hershberg et al. 2017). STIDAT distributed as-is and as-available, with no warranties, under the Creative Commons Attribution 4.0 International License (https://creativecommons.org/licenses/by/4.0/legalcode).

Appendix K Protocol Amendment History

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

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Protocol J2G-GH-JZJK	30-Jul-2019

Amendment [a]: (20 July 2020)

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
Synopsis, and 3.4 Investigational Plan	Enrollment in Cohort 1 was clarified as "For lung cancer, only patients harboring *RET-KIF5B, RET-CCDC6, RET-NCOA4* can be enrolled in Cohort 1. For other solid tumor, patients with any *RET* fusion can be enrolled in Cohort 1". Added inclusion criteria to Cohort 3 as "Other *RET*-altered solid tumor or other *RET* alteration/activation not meeting the requirements for Cohorts 1 or 2".	Clarification
Synopsis, and 4.1 Inclusion Criteria	Add additional information to clarify calculation of eGFR.	Clarification
Synopsis, and 4.2 Exclusion Criteria	Metastases was clarified as symptomatic CNS metastases in exclusion criterion 26. "Lower limit of detection of the assay" was updated to "upper limit of detection of the assay" in Exclusion Criterion 29; removed exclusion criterion 34 and 35.	Clarification
1.1 Tumors with *RET* Abnormalities and Current Treatment Options, 1.4 Determination Starting Dose	Updated related contents per latest IB.	To be consistent with IB version 7.0
1.5 Clinical Experience	Updated new data of LIBRETTO-001 study.	To be consistent with IB version 7.0
1.6.1 Known and Anticipated Risks	Replaced risks based on animal studies with risks based on clinical studies.	To be consistent with IB version 7.0

Section # and Name	Description of Change	Brief Rationale
1.6.2 Potential Drug Interactions, 6.3.3 Other Concomitant Medications, Appendix D and Appendix E	Updated drug interaction part and concomitant medication guidance per latest IB.	To be consistent with IB version 7.0
4.1 Inclusion Criteria	Removed "requirement may be waived with Sponsor approval" for archived tumor tissue sample notes.	Clarification
6.2.1 General Dosing Instructions, 6.2.4 Dose Delays and Modifications	Added additional information when re-escalation to a prior dose level after a dose reduction is permitted. Add additional information for dose modifications for hypersensitivity, LFT abnormalities, thrombocytopenia, and hypertension.	Clarification and to be consistent with IB version 7.0
6.2.4 Dose Delays and Modifications, and 8.2.2.1 Hepatic Safety Monitoring	Clarified LFTs included AST, ALT, ALP, and total and direct bilirubin; modified dose modification guidance for special adverse events, including hypersensitivity, liver function test abnormalities, thrombocytopenia, and hypertension.	To be consistent with IB version 7.0
Table 6-1 Suggested Toxicity Management for all Parts of this Study	The starting dose for thrombocytopenia was updated from 80 mg to 120 mg.	Clarification
6.3.3 Other Concomitant Medications	Clarified herbal products were with anti-cancer activity; added language for concurrent use of steroids.	Clarification; to be consistent with IB version 7.0
7 Tests and Evaluations	Added additional information for timing of routine laboratories and procedures and clarified "routine evaluations performed within -2 days of the visit day will not be considered protocol deviations".	Clarification
Table 7-1 Schedule of Activity (SoA)	Added Serum chemistries in C1D8±2 Days, Survival in SFU (D28±7 days).	Clarification
Table 7-1 Schedule of Activity (SoA) note "a"	The duration of ±7 days was updated to +7 days in the explanation of EOT, and added additional information for lab testing performed ≤7 days prior to EOT.	Clarification

Section # and Name	Description of Change	Brief Rationale
Table 7-1 Schedule of Activity (SoA) note "h"	Added respiratory rate to vital signs.	Clarification
Table 7-1 Schedule of Activity (SoA) note "i", 7.2 Cycle 1, and 7.3 Cycles 2 and Higher	C1D15 was updated to C1D15, Day 1 of C2-higher, and clarified vital signs should be performed prior to PK collection. Removed tests in Day 1 of C2-C6 and all other clinic visits when neither PK nor ECGs are being collected.	Clarification
Table 7-1 Schedule of Activity (SoA) note "j", and 7.2 Cycle 1	C1D8 and thereafter was updated to C1D8, C2D1 and thereafter for ECG test, and clarified an extra ECG should be timed prior to PK collection on C1D8.	Clarification
Table 7-1 Schedule of Activity (SoA) note "l"	Added a window of -2 days to Day 1 of every cycle, and added additional information for screening testing performed ≤7 days prior to C1D1.	Clarification
Table 7-1 Schedule of Activity (SoA) note "o", 7.2 Cycle 1	Added a window of -2 days to C2D15 and C3D15.	Clarification
Table 7-1 Schedule of Activity (SoA) note "p"	Added additional information for coagulation testing to avoid repeat testing.	Clarification
Table 7-1 Schedule of Activity (SoA) note "v", 7.1 Screening Period, and Appendix G. Tumor Measurements and Assessment of Disease Response using RECIST version 1.1	Removed "chest CT does not require IV contrast" for IV and oral contrast.	Clarification
Table 7-1 Schedule of Activity (SoA) note "z", and 8.4 Pharmacokinetics	Added hours (±15 minutes) to 1 and 2.	Clarification
Table 7-1 Schedule of Activity (SoA) note "bb"	Patient bowel diary was clarified to be answered by the subject to the best of his/her ability	Clarification

Section # and Name	Description of Change	Brief Rationale
7.1 Screening Period	Removed repeated information in Screening Period.	Clarification
7.2 Cycle 1	Clarified ECG testing should be performed before PK collection on C1D8.	To be consistent with Table 7-1 notes "j"
7.3 Cycles 2 and Higher	Clarified urinalysis to be performed D1 C2, and as clinically indicated; Adjusted order of safety part.	To be consistent with Table 7-1; Clarification
7.4 End of Treatment Visit (All Patients)	Removed limitations to "Resting 12-lead ECG".	Clarification
7.5 Safety Follow-up Visit (SFU)	Added limitations to "Resting 12-lead ECG" with "only if prior ECG reading showed treatment-emergent abnormalities".	Clarification
8.1.1 Imaging	Added descriptions for bone scan.	Clarification
8.2.2.1 Hepatic Safety Monitoring	Added AST testing instead of ALT only, and added language for participants with baseline ALT/AST ≥1.5X ULN; removed Appendix H in brackets.	To be consistent with IB version 7.0; the content is not available in Appendix H.
8.7 Medical Resource Utilization and Health Economics	Replaced electronic versions of the questionnaires with paper source document, and removed related language.	Clarification
10.3.2 Committees Structure	Deleted "blinded" for independent central review.	Clarification
Appendix H. Clinical Laboratory Tests	Clarified all safety related laboratory tests were performed in local labs, and made minor formatting/ editorial changes.	Clarification
Throughout	Updated the name of LOXO-292 to selpercatinib	Clarification
Throughout	Updated all T3 and T4 to FT3 and FT4, respectively.	Clarification

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