Protocol J2G-OX-JZJA (12)

A Phase 1/2 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 (LIBRETTO-001)

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CLINICAL PROTOCOL LOXO-RET-17001 (J2G-OX-JZJA)

A Phase 1/2 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 (LIBRETTO-001)

Investigational Product:	Selpercatinib (LY3527723)
Protocol Number:	LOXO-RET-17001 (J2G-OX-JZJA)
Development Phase:	1/2
IND #:	133193
EudraCT #:	2017-000800-59
EU Trial #:	2023-507702-13-00
Sponsor:	Loxo Oncology, Inc., a wholly owned subsidiary of Eli Lilly and Company

Approval Date: Protocol Amendment 12.0 Electronically Signed and Approved by Lilly on date provided below.

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Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Version 11.0	20 October 2022
Version 10.0	19 October 2021
Version 9.0	03 June 2020
Version 8.0	10 June 2019
Version 7.0	18 October 2018
Version 6.0	11 September 2018
Version 5.0	30 May 2018
Version 4.0	20 November 2017
Version 3.0	20 July 2017
Version 2.0	27 March 2017
Version 1.0	01 March 2017

Amendment [12.0]

This amendment is considered to be substantial.

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

Overall Rationale for the Amendment:

The purpose of this amendment is to consolidate the Germany and Denmark country-specific addenda into Appendix K, minor clarifications/corrections, update as per the latest Investigator Brochure, and to align with EU Clinical Trial Regulation (EU-CTR) requirements.

Section # and Name	Description of Change	Brief Rationale
Synopsis	• Shortened • Added EU Trial Number • Added Eligibility Criteria • Added Ethical considerations of Benefit/Risk	To align to EU-CTR format
	Phase 2 – corrected seven cohorts to six cohorts	Correction
List of Abbreviations and Definitions of Terms	Updated abbreviations and definitions	To align with EU-CTR format

Section # and Name	Description of Change	Brief Rationale
3.6 Phase 2	• Phase 2 – corrected seven cohorts to six cohorts • Cohort 7 removed from Figure 3-1 Study Schema	For accuracy, as Cohort 7 was removed from the study as of 01 June 2022
4.1 Inclusion Criteria for Phase 1	Inclusion Criterion [3]: removed reference to Section 4 in notes	Clarification
4.2. Inclusion Criteria for Phase 2	Inclusion Criterion [7] removed	For accuracy, as Cohort 7 was removed from the study as of 01 June 2022
6.1 Investigational Product	Removed 20 mg/mL oral suspension	Oral suspension no longer provided
	Clarification to extenuating circumstances to include "where allowed by regional regulatory authorities"	Clarification
	• Added statement about EU authorization. • Added "Packaging and Labeling"	To align to EU-CTR format
6.2.4. Dose Delays/Modifications	Updated dose modification guidance for • Interstitial Lung Disease/Pneumonitis • Chylothorax and Chylous Ascites	As per updated Investigator Brochure
Table 7-1 Schedule of Assessments	Corrected Footnote q: urinalysis is only required beyond cycle C1D15 if clinically indicated	Correction
7.3. Cycles 2 and Higher	Urinalysis – removal of "Day 1 of each cycle starting with C2"	Correction
7.8. Procedures for Special Tests	Section 7.8.7 added for Thyroid function	As per updated Investigator Brochure

Section # and Name	Description of Change	Brief Rationale
8.2. Analysis Populations	Added a paragraph on handling of missing, unused, and spurious data	To align with EU-CTR format
9. Adverse Events	Events meeting AE definition added	To align with EU-CTR format
9.4.1. Serious Adverse Event Reporting – Procedures for Investigators: Initial Report	Added SAE Regulatory Reporting	To align with EU-CTR format
10.1. Regulatory and Ethical Considerations	Added statement about reporting of significant issues related to participant's safety, rights, and data integrity	To align with EU-CTR format
10.2. Data Management	Added a subsection on "Data Protection"	To align with EU-CTR format
10.4. Termination	Added required language on "Reports"	To align with EU-CTR format
Appendix K Country-Specific Requirements	Germany: Consolidation of Germany-specific protocol addendum into Appendix K	For harmonization of the protocol and to avoid country and region-specific protocol versions in the EU
	Denmark: Consolidation of Denmark-specific protocol addendum into Appendix K	For harmonization of the protocol and to avoid country and region-specific protocol versions in the EU
Throughout the protocol	Minor editorial revisions	Clarification

SYNOPSIS

TITLE:

A Phase 1/2 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 (LIBRETTO-001)

PROTOCOL NUMBER:

LOXO-RET-17001 (J2G-OX-JZJA)

EudraCT #: 2017-000800-59

EU Trial #: 2023-507702-13-00

OBJECTIVES:

Primary Objective (Phase 1):

- To determine the maximum tolerated dose (MTD)/recommended Phase 2 dose (RP2D) of selpercatinib.

Secondary Objectives (Phase 1):

- To determine the safety profile and tolerability of selpercatinib.
- To characterize the pharmacokinetic (PK) properties of selpercatinib.
- To assess the anti-tumor activity of selpercatinib by determining objective response rate (ORR) using Response Evaluation in Solid Tumors Version 1.1 (RECIST 1.1) or Response Assessment in Neuro-Oncology (RANO), as appropriate to tumor type.

Primary Objective (Phase 2):

- To assess, for each Phase 2 expansion cohort, the anti-tumor activity of selpercatinib by determining ORR using RECIST 1.1 or RANO, as appropriate for tumor type, as assessed by independent review committee (IRC).

Secondary Objectives (Phase 2):

- To assess, for each expansion cohort, the anti-tumor activity of selpercatinib by determining:
  - ORR based on RECIST 1.1 or RANO, as appropriate to tumor type, as assessed by Investigator;
  - Best change in tumor size from baseline as assessed by IRC and Investigator;
  - Duration of response (DOR) as assessed by IRC and Investigator;
  - Central nervous system (CNS) ORR based on RECIST 1.1 or RANO, 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 any and best response based on RECIST 1.1 or RANO, 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.

STUDY DESIGN:

This is an open-label, multi-center Phase 1/2 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). This study includes two parts: Phase 1 (dose escalation) and Phase 2 (dose expansion). Patients with *RET* alterations in tumor and/or blood will be identified through molecular assays,

as performed in the routine course of clinical care. The *RET* alteration result should be generated from a laboratory with certification by Clinical Laboratory Improvement Amendments (CLIA), International Organization for Standardization/Independent Ethics Committee (ISO/IEC), College of American Pathologists (CAP), or other similar certification as per local guidelines including but not limited to In Vitro Diagnostic Regulation (IVDR) compliance as applicable. The Sponsor should be contacted to discuss test results to ensure trial eligibility.

Phase 2:

A dose of 160 mg BID has been selected by the SRC as the recommended Phase 2 dose (RP2D). Therefore, up to ~875 patients with advanced solid tumors 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 six Phase 2 cohorts (refer to Study Schema).

Eligibility Criteria:

- Patients with a locally advanced or metastatic solid tumor who:
  - have progressed on or are intolerant to standard therapy
  - no standard therapy exists
  - 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.
- Have a *RET* gene alteration identified through molecular assays at a laboratory with CLIA, ISO/IEC, CAP or other similar, either from tumor or blood.
- Patients with additional validated oncogenic driver that could cause resistance to selpercatinib treatment are not eligible.
- Measurable or non-measurable disease as determined by RECIST 1.1 or RANO as appropriate to tumor type.
- At least 18 years of age, or at least 12 years of age for countries and sites where approved.
- Eastern Cooperative Oncology Group performance status score of 0, 1, or 2.
- Archived tumor tissue sample available.

ETHICAL CONSIDERATIONS OF BENEFIT/RISK:

Patients with *RET*-fusion positive cancers (NSCLC, papillary thyroid cancer, colon, others) and *RET*-mutant cancers (MTC) represent populations with high unmet need. Available therapies for these patients provide short-term palliation (i.e., chemotherapy), may be less effective in cancers driven by kinase fusions (i.e., immunotherapy) and/or are very toxic (i.e., multikinase inhibitors). 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 indicate the benefit/risk ratio for selpercatinib in this study is favorable.

PLANNED SAMPLE SIZE:

Phase 1: ~15 patients for each dose cohort in order to define the MTD/recommended dose for further study of selpercatinib for a total of ~120 patients.

Phase 2: up to ~875 patients.

STATISTICAL METHODS:

Safety Analyses:

The Safety Analysis Set 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.

An SRC will be established to oversee the safety aspects of the Phase 1 portion of the study. The SRC will perform ongoing review of SAEs and other safety-related data throughout the conduct of the study. For Phase 1, the SRC will be convened for each dose escalation decision or as needed. For Phase 2, the SRC will convene at a minimum of every 6 months.

Efficacy Analyses:

The efficacy analysis will be conducted on the Safety Analysis Set - patients with at least 6 months of treatment from the first dose of selpercatinib. These analyses will be summarized per tumor indication, including patients from both the Phase 1 and Phase 2 portions A Statistical Analysis Plan (SAP) will provide specific details on the efficacy analysis set.

ORR will be estimated for tumor indication based on the observed proportion of patients whose best overall response, based on RECIST 1.1 or RANO, 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% confidence interval (CI). Waterfall plots will be used to depict graphically the maximum decrease from baseline in the sum of longest diameters of target lesions. The duration of objective response, PFS, and OS will be summarized descriptively for each cohort using the Kaplan-Meier method.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation or Term	Definition
abuse	use of a study intervention for recreational purposes or to maintain an addiction or dependence
AE	adverse event
ACTH	adrenocorticotropic hormone
ALK	anaplastic lymphoma kinase
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
anti-PD-1	anti-programmed cell death protein 1
AST	aspartate aminotransferase
ATP	adenosine triphosphate
AUC	area under the concentration versus 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
BCRP	breast cancer resistance protein
BID	twice daily
BUN	blood urea nitrogen
BSA	body surface area
C	Cycle
CAP	College of American Pathologists
CBR	clinical benefit rate
CDMS	Clinical Data Management System
CEA	carcinoembryonic antigen
cfDNA	circulating free tumor deoxyribonucleic acid
CI	confidence interval
CL/F	apparent oral clearance of drug
CLIA	Clinical Laboratory Improvement Amendments
C_{max}	maximum drug concentration
C_{min}	minimum drug concentration
CNS	central nervous system
CR	complete response
CT	computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events

Abbreviation or Term	Definition
CYP	Cytochrome P450
CYP3A4	Cytochrome P450 3A4
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
FISH	Fluorescence In Situ Hybridization
FLAIR/T2	T2-weighted fluid-attenuated inversion recovery
GCP	Good Clinical Practices
GDPR	EU General Data Protection Regulation
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
IC_{90}	90% inhibitory concentration
ICF	informed consent form
ICH	International Conference on Harmonisation
ICH GCP	International Conference on Harmonisation-Good Clinical Practices
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product (see also "investigational product")

Abbreviation or Term	Definition
	A medicinal product which is being tested or used as a reference, including as a placebo, in a clinical trial.
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
IVDR	In vitro diagnostic regulation
KRAS	Kirsten rat sarcoma virus oncogene
LDH	lactate dehydrogenase
LFT	liver function test
LHRH	luteinizing hormone-releasing hormone
LOXO-292	investigational product; selpercatinib
LPS	Lansky Performance Score
LTFU	Long-Term Follow-Up
MedDRA	Medical Dictionary for Regulatory Activities
medication error	Errors in the prescribing, dispensing, or administration of a study intervention, regardless of whether or not the medication is administered to the participant or the error leads to an AE. Medication error generally involve a failure to uphold one or more of the five “rights” of medication use: the right participant, the right drug, the right dose, right route, at the right time. In addition to the core five rights, the following may also represent medication errors: • dose omission associated with an AE or a product complaint • dispensing or use of expired medication • use of medication past the recommended in-use date • dispensing or use of an improperly stored medication • use of an adulterated dosage form or administration technique inconsistent with the medication's labeling (for example, Summary of Product Characteristics, IB, local label, protocol), or • shared use of cartridges, prefilled pens, or both.
misuse	Use of a study intervention for self-treatment that either is inconsistent with the prescribed dosing regimen, indication, or both, or is obtained without a prescription
mg	milligram
MHC-I	Major Histocompatibility Complex class I
MKIs	multikinase inhibitors
MRI	magnetic resonance imaging
MTC	medullary thyroid cancer
MTD	maximum tolerated dose
mRNA	messenger ribonucleic acid

Abbreviation or Term	Definition
MRSD	maximum recommended starting dose
NCI	National Cancer Institute
NCI CTCAE	National Cancer Institute's 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	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
PO	per os (oral)
PP	Per-protocol Analysis Set
PPI	proton pump inhibitors
PR	partial response
PRO	patient-reported outcomes
PTC	papillary thyroid cancer
Q12W	every 12 weeks
QD	once daily
QTc	corrected QT interval
QTcF	QT interval corrected for heart rate (Fridericia's formula)
QTcI	individual animal heart rate corrected QT intervals
RANO	Response Assessment in Neuro-Oncology
RBC	red blood cell
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

Abbreviation or Term	Definition
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 Refers to an adverse event that occurs in a clinical trial participant, which is assessed by the sponsor and or study investigator as being unexpected, serious and as having a reasonable possibility of a causal relationship with the study intervention
$t_{1/2}$	terminal elimination half-life
T_3	triiodothyronine
T_4	Thyroxine
TBD	to be determined
TEAE	treatment-emergent adverse event
TKIs	tyrosine kinase inhibitors
T_{max}	time to maximum plasma concentration
TSH	thyroid-stimulating hormone
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

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 next-generation sequencing (NGS) approaches to a large collection of human tumors has led to the identification of *RET* gene fusions in a small fraction (1–2%) 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-positive NSCLC, *RET*-mutant MTC, and other cancers with RET activation could benefit from potent and selective RET kinase inhibition.

Highly selective tyrosine kinase inhibitors (TKIs) that inhibit RET are lacking, but 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 of only 3.6–7.3 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 in patients, 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, while anti-programmed cell death protein 1 (anti-PD-1) monoclonal antibodies (e.g., nivolumab, pembrolizumab), which have recently been approved for NSCLC patients, may be less effective in tumors marked by single-gene driver oncogenic kinase alterations (including kinase fusions) with otherwise low mutational burdens and low neo-antigen production (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 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 1/2 study of selpercatinib is required to understand the PK, safety, and maximum tolerated dose (MTD) for selpercatinib in patients and to permit the preliminary assessment of efficacy.

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. In the 3-month repeated-dose study, an increase in QTc interval was noted in female minipigs administered 5 mg/kg/day of selpercatinib, but the degree of the increase was small (approximately 7 to 12%). These low magnitude QTc changes were potentially selpercatinib-related, but were not considered adverse.

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 detail is provided in the selpercatinib Investigator's Brochure (IB).

In an additional study in juvenile rats, changes in bone observed at therapeutically relevant exposures included increased physeal thickness of multiple bones, characterized by hypertrophy, hyperplasia, and dysplasia which resolved during the recovery phase and decreases in femur length observed at recovery, indicative of impaired longitudinal bone growth.

Additional information on the nonclinical pharmacology, PKs, and toxicity of selpercatinib are provided in the selpercatinib IB.

1.4 Rationale for Enrolling Patients Younger than Age 18 Years

The rationale for inclusion of patients younger than 18 years (where allowed by the Institutional Review Board [IRB]/Research Ethics Board [REB]/Independent Ethics Committee [IEC]) is the crucial role of RET mutations and fusions in the pathogenesis of thyroid cancer in younger patients. Germline *RET* gene mutations account for the majority of patients with hereditary MTC syndromes, and patients may develop cancer as children or adolescents (Castinetti, Moley et al. 2017). In addition, a recent report described a surprisingly high frequency of *RET* gene fusions (22%) in pediatric patients with PTC in the Northeast United States (US) (Prasad, Vyas et al. 2016). In this study, all RET-fusion patients were between the ages of 13 to 18 years, and the presence of a *RET* fusion was associated with high-risk pathologic features, including larger size, diffuse thyroid involvement, lympho-vascular invasion, and metastasis. Limited available clinical data suggests moderate efficacy and significant toxicity for such patients when treated with MKIs (Robinson, Paz-Ares et al. 2010).

In vitro data show that selpercatinib is metabolized primarily by cytochrome P450 3A4 (CYP3A4). CYP3A4 is expressed at a very low level at birth; it increases to adult levels at approximately 2 years of age (Wildt, Johnson et al. 2003). Thus, well before age 12, CYP3A4 has reached its adult level of expression, as have most drug clearance mechanisms. Furthermore, a recent review of 126 products with at least one pediatric trial completed under the Food and Drug Administration (FDA) in 2007 identified 92 products with adolescent indications concordant with adult indications. Of these 92 products, 87 (94.5%) have identical adolescent and adult dosing (Momper, Mulugeta et al. 2013). Thus, the dose level for patients age 12 to 17 years in this study will be the same as their adult counterparts.

The nonclinical bone-related findings suggest a potential risk for growth plate abnormalities in patients with open growth plates, the impact of which could include decreased longitudinal bone growth. No clinically significant findings have been identified in the small number of patients under age 18 enrolled in selpercatinib clinical trials to date. However, participants who have not yet obtained full adult height are recommended to undergo growth plate monitoring.

As described in Section 9.1, a Safety Review Committee (SRC) will be established to oversee the safety aspects of the study. Additional meetings will be held after every fifth patient between the ages of 12 to 17 years (inclusive) is enrolled.

1.5 Benefit/Risk

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 cautious dose escalation, 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 cancers (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), 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 indicate the benefit/risk ratio for selpercatinib in this study is favorable.

1.6 Determination of Recommended Starting Dose

The maximum recommended starting dose (MRSD) was established as 44 mg/day based on the FDA's guidance "Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers" (2015) (US-FDA 2005) and the actual starting dose was 20 mg/day, given once daily. Additional information is provided in the selpercatinib IB.

1.7 Clinical Experience

As of May 8, 2022, a total of 821 of the 825 (99.5%) patients treated in this study (LOXO-RET-17001 [J2G-OX-JZJA]) experienced at least 1 treatment-emergent adverse event (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 the 9 dose levels ranging from 20 mg to 480 mg (240 mg twice daily [BID]) daily, most TEAEs were mild or moderate (Grade 1 or 2) in severity. The most frequently reported AEs of special interest are listed in Section 1.7.1.

Refer to the selpercatinib IB for the most current summary of clinical experience including anticipated risks and dose modification plans for specific AEs.

1.7.1 Known and Anticipated Risks

As of a clinical data cut-off (May 8, 2022) for this study (LOXO-RET-17001 [J2G-OX-JZJA]), the following AEs of special interest include:

- Dry mouth (48.7% total, 38.4% related)
- Hypertension (41.5% total; 28.7% related)
- AST increased (37.8% total; 28.8% related)
- ALT increased (36.2% total; 29.1% related)
- Electrocardiogram QT prolonged (20.5% total, 16.1% related)

Additional details on the safety profile of selpercatinib are provided in the selpercatinib IB.

1.7.2 Potential Drug Interactions

Selpercatinib has pH-dependent solubility and its PK can be affected by agents that modify gastric pH such as 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. Additional guidance is provided in the selpercatinib IB.

Selpercatinib is metabolized predominantly by CYP3A4. Following oral administration of a single radiolabeled 160 mg dose of selpercatinib to healthy subjects, unchanged selpercatinib constituted 86% of the radioactive drug components in plasma. In addition, coadministration of selpercatinib with sensitive CYP3A4 substrates or CYP2C8 substrates may increase their plasma concentrations, which may increase the incidence or severity of adverse reactions. Coadministration of selpercatinib with strong and moderate CYP3A inhibitors, strong and moderate CYP3A inducers, and CYP2C8 and CYP3A substrates should be avoided. Additional guidance is provided in the selpercatinib IB.

Selpercatinib inhibits drug transporter substrates 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. 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 (Phase 1)

- To determine the MTD/recommended Phase 2 dose (RP2D) of selpercatinib.

2.2 Secondary Objectives (Phase 1)

- To determine the safety profile and tolerability of selpercatinib.
- To characterize the PK properties of selpercatinib.
- To assess the anti-tumor activity of selpercatinib by determining objective response rate (ORR) using Response Evaluation in Solid Tumors Version 1.1 (RECIST 1.1) or Response Assessment in Neuro-Oncology (RANO), as appropriate to tumor type.

2.3 Primary Objective (Phase 2)

- To assess, for each Phase 2 expansion cohort, the anti-tumor activity of selpercatinib by determining ORR using RECIST 1.1 or RANO, as appropriate to tumor type, as assessed by independent review committee (IRC).

2.4 Secondary Objectives (Phase 2)

- To assess, for each expansion cohort, the anti-tumor activity of selpercatinib by determining:

  ORR based on RECIST 1.1 or RANO, as appropriate to tumor type, as assessed by Investigator;
  Best change in tumor size from baseline as assessed by IRC and Investigator;
  Duration of response (DOR) as assessed by IRC and Investigator;
  Central nervous system (CNS) ORR based on RECIST 1.1 or RANO, as appropriate for tumor type, as assessed by IRC (for patients with brain metastases);
  CNS DOR as assessed by IRC (for patients with brain metastases);
  Time to any and best response based on RECIST 1.1 or RANO, as appropriate for 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.

2.5 Exploratory Objectives (Phase 1 and Phase 2)

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 with selpercatinib.

To characterize *RET* gene fusions and mutations and concurrently activated oncogenic pathways by molecular assays, including NGS from tumor biopsies and circulating free tumor DNA (cfDNA).

To collect patient-reported outcomes (PRO) data to explore disease-related symptoms and health-related quality of life (HRQoL).

3. INVESTIGATIONAL PLAN

3.1 Study Design

This is an open-label, multi-center Phase 1/2 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). This study includes two parts: Phase 1 (dose escalation) and Phase 2 (dose expansion).

Patients with *RET* alterations in tumor and/or blood will be identified through molecular assays, as performed in the routine course of clinical care. The *RET* alteration result should be generated from a laboratory with certification by Clinical Laboratory Improvement Amendments (CLIA), International Organization for Standardization (ISO)/IEC, College of American Pathologists (CAP), or other similar certification as per local guidelines including but not limited to In Vitro Diagnostic Regulation (IVDR) compliance as applicable. The Sponsor should be contacted to discuss test results to ensure trial eligibility.

Both Phase 1 and Phase 2 will consist of a screening period, a treatment period, 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 progressive disease [PD]), disease status, survival, and subsequent anticancer therapy(ies) will be assessed during LTFU.

Selpercatinib will be administered in oral form, once daily (QD) or BID, depending upon cohort assignment. 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 meets criteria requiring discontinuation of treatment (refer to Section 6.4 Removal of Patients from Therapy or Assessment). 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.

This study will be considered complete (that is, the scientific evaluation will be complete [study completion]) once it has been determined by the Sponsor that the evaluation of efficacy and safety of the populations of interest are sufficient and complete. Investigators will continue to follow the study schedule for all patients until notified that study completion for that patient/cohort has occurred. Patients who are still on study intervention at the time of study completion may continue to receive study intervention (continued access) if they are experiencing clinical benefit and no undue risks (as determined by the investigator). The

continued access period begins after study completion and will continue until the end of study (refer to Section 7.9).

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 completes any applicable continued access follow-up, or
- consent has been withdrawn, or
- is lost to follow-up, or
- has died, or
- has transferred to a separate study to receive further medication or treatment continuation has been secured by other means.

3.3 General Treatment Procedures

Patients will receive the assigned selpercatinib dose on Cycle (C) 1 Day (D) 1 in accordance with the cohort assignment. Cycles are measured in 28-day increments and the dose limiting toxicity (DLT) observation period during Phase 1 comprises the first 28 days of treatment during C1. During this time, blood samples for drug levels will be collected and patients will be monitored for safety.

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, 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. 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.

3.4 Phase 1 and Maximum Tolerated Dose Determination

During Phase 1, patients with advanced cancer are initially eligible if they have progressed on or are intolerant to available therapies, or no standard or available curative therapy exists, or in the opinion of the Investigator, they would be unlikely to tolerate or derive significant clinical benefit from appropriate standard of care therapy, or they declined standard therapy. Treatment

with any number of prior therapies, including any number of prior MKIs with anti-RET activity, is allowed (see Appendix A for examples). However, prior treatment with a selective RET inhibitor is prohibited (including investigational selective RET inhibitors).

Preclinical data indicate that a selpercatinib plasma level of 70 ng/mL is equivalent to the IC_{50} for RET (corrected for human plasma protein binding). Therefore, once a dose level is achieved that: (1) is associated with a DLT rate of < 33%; (2) is deemed safe by the SRC; and (3) is associated with a minimum drug concentration (C_{min}) of > 70 ng/mL at steady state in ≥ 70% of patients in the same dosing cohort (e.g., 3/3, 3/4, 4/5, 5/6 patients, etc.), enrollment to subsequent dose levels during dose escalation will be restricted to patients with: (1) *RET* fusion-positive solid tumors; (2) MTC; (3) an advanced solid tumor that harbors a *RET* gene alteration (excluding synonymous, frameshift, or nonsense mutations); or (4) with prior Sponsor approval, an advanced solid tumor with other evidence of RET activation (refer to Section 4). A positive germline DNA test for a *RET* mutation is acceptable for patients with MTC. *RET* gene alterations in tumor tissue and/or blood will be identified through molecular assays, as performed for clinical evaluation. The *RET* alteration result should be generated from a laboratory with CLIA, ISO/IEC, CAP, or other similar certification as per local guidelines including but not limited to IVDR compliance as applicable. The Sponsor should be contacted to discuss test results from labs where such certification is not clearly demonstrated to determine eligibility.

The starting dose of selpercatinib in oral capsule form is 20 mg/day (e.g., 20 mg QD). Should the observed human exposure match that predicted by modeling based on in vitro and animal data, this starting dose is likely to provide some degree of RET target engagement in patients without compromising patient safety.

Dose escalations will be in increments of 100% above the previous dose level for the first 3 dose escalations. After the third dose increase, a modified Fibonacci dose escalation (Penel and Kramar 2012) will be employed for any subsequent dose escalations, with increments of ~67%, ~50%, and ~33%. Additional dose escalations, if needed, will be with increments of ~33%. Each dose level after the starting dose represents the maximum dose to which patients will be escalated, and no individual dose escalation will be more than twice the dose at the previous level. However, the actual dose escalated to may be modified by the SRC to be compatible with the capsule strengths available and to minimize capsule burden for patients, while maintaining the modified Fibonacci design.

The dose escalation scheme will revert to a modified Fibonacci design (i.e., without further 100% increments initially specified for the first three dose escalations) if either of the following are observed (whichever occurs first): (1) the occurrence of two or more treatment-related Common Terminology Criteria for Adverse Events (CTCAE) Grade 2 toxicities within a dosing cohort; or (2) a dose level is achieved that is consistent with causing RET target engagement (refer to Section 4.1 for target exposure). The actual dose levels used in this ongoing study are indicated in Table 3-1.

Table 3-1 Actual Dose Escalations for Selpercatinib

Level	Dose	Frequency	Total Daily Dose
1	20 mg	QD	20 mg
2	20 mg	BID	40 mg
3	40 mg		80 mg
4	60 mg		120 mg
5	80 mg		160 mg
6	120 mg		240 mg
7	160 mg		320 mg
8	240 mg		480 mg
9	200 mg		400 mg
Additional potential doses			
10 and higher	Per SRC	TBD	TBD

Abbreviations: BID-twice daily; mg-milligram; QD-once daily; SRC-Safety Review committee; TBD-to be determined.

A meeting of the SRC will be convened for each cohort dose escalation decision (see Section 9.1). For each cohort dose escalation decision, the SRC will recommend the dose for escalation, determination of DLT(s) recommended dose for further study. Smaller dose escalation increments will be considered in the event of frequent, unexpected AEs or DLTs as noted below.

A minimum of 3 patients in a given cohort must have completed 28 days of safety assessment in C1 without DLT, and a maximum of one DLT may be seen in 6 patients who have completed the DLT window before the next cohort initiates accrual.

Dose escalation will follow the 3+3 design. A minimum of 3 and a maximum of 6 persons will be concurrently enrolled into a single dosing cohort, depending on the occurrence of DLTs.

Each patient in a given cohort must have completed safety assessments through the first 28 days of treatment in C1, and received a minimum of 75% (e.g., 42/56 doses with BID dosing) of the planned total dose during that time (unless due to toxicity) to be eligible for the assessment of a DLT. Patients who receive less than 75% of planned doses due to reasons other than a DLT will be replaced for the determination of the MTD but will remain part of the safety population if they received at least one dose of study drug.

If 3 patients in a dosing cohort are evaluable for toxicity (i.e., have completed 28 days of safety assessment in C1 and have received at least 75% of planned doses) and no DLT has been observed, the next three patients may be enrolled to the next higher dose level with approval of the SRC.

If one patient within a three-person dosing cohort experiences a DLT, then a total of 6 patients will be enrolled to that cohort for the purposes of DLT evaluation. If none of the additional patients have a DLT (i.e., 1 of 6 patients), then enrollment to the next higher dose level may

begin with approval of the SRC. If ≥ 2 patients within a dose escalation cohort experience a DLT, then the DLT Dose Level has been reached, and dose escalation will be stopped.

The MTD is defined as the highest dose level at which none of the first 3 treated patients, or not more than 1 of the first 6 treated patients, experiences a DLT. Therefore, if two or more patients (≥ 33%) at the same dose level experience a DLT, then further enrollment to that cohort will stop and the cohort data will be reviewed by the SRC. In order for the MTD to be accurately determined, the SRC will evaluate whether the dose level previous to the dose level at which ≥ 33% of patients experience a DLT will be considered the MTD, whether an intermediate dose level or a different dosing frequency should be evaluated, and/or whether additional patients need to be evaluated at this dose level if the DLTs seen at this dose level are considered to be not serious or can be reasonably attributed to the patient's underlying disease, other medical conditions, or concomitant medications, rather than to selpercatinib.

During the dose escalation phase, selected cohorts previously declared safe by the SRC may be expanded to a total of approximately 15 patients to further investigate the tolerability, PK and biological activity of selpercatinib. These additional patients will have confirmed *RET* status, and priority will be given to patients with *RET* alterations as defined in Table 3-3. The SRC will continue to monitor the cumulative safety data from the cohorts previously declared safe and the current dose cohort under evaluation. Enrollment of patients to the current dose cohort under evaluation will take precedent.

There may be situations indicated by safety, efficacy, or PK that warrant exploration of additional, lower dose levels not specified in (or by the dose levels after an earlier switch to a modified Fibonacci design as a result of meeting criteria 1 or 2 above). These include the occurrence of frequent, unexpected AEs; frequent DLTs (e.g., DLTs that occur in more than one dose level, though at a rate < 33% in the any one dose level); or PK considerations. The occurrence of any of these may warrant consideration of smaller dose escalation increments than specified above or a change in dose schedule. Therefore, each dose level specified in Table 3-1 (or by an earlier institution of a modified Fibonacci design) is the maximum dose to which patients will be escalated to at that level. Prior to enrollment of the first patient at each level, the actual dose escalated to may be lowered or the dosing schedule may change upon review of safety and available PK data by the SRC, to minimize the risk of toxicity for patients, more closely characterize DLT(s), and/or more accurately identify the MTD.

Escalation will proceed through all dose levels or until the SRC and the Sponsor determine that a suitable dose has been achieved based on available data (safety, PK exposure, clinical activity).

After completion of the 28-day DLT period in C1, intra-patient dose escalation may be permitted by the Sponsor, provided that the patient is tolerating their current dose and the dose level to which the patient will be escalated has already been evaluated, has a DLT rate of < 33%, and has been declared safe by the SRC. Refer to Section 7.4 for required assessments for intra-patient dose escalation.

The participant enrollment schema is summarized in Table 3-2.

Table 3-2 Selpercatinib Participant Enrollment Schema for Dose-Limiting Toxicity (DLT) Evaluation

Criteria	3+3
Minimum number of patients per cohort	3
Maximum number patients per cohort	6*
Criteria to increase from 3 to 6 patients	1/3 DLTs
Criteria to escalate dose	0/3 DLTs OR 1/6 DLTs
Criteria to stop dose escalation	≥ 2 DLTs
Criteria to de-escalate dose cohort	≥ 2 DLTs at current dose level and < 33% DLT rate in previous dose level
Maximum tolerated dose	≤ 1/6 DLTs

*See above for situations warranting accrual of additional patients.

3.5 Dose-Limiting Toxicity (DLT) Definition

A DLT is defined as any of the TEAEs (a TEAE is defined as an AE that starts on or after the first administration of study medication) listed below, as defined by the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 4.03 (NCI CTCAE v4.03), occurring during the first 28 days of treatment, provided that the participant has received at least 75% of planned doses and the AE is not reasonably attributed to the patient's underlying disease, other medical conditions, or concomitant medications. The DLT definitions are:

Grade 3 hematologic or non-hematologic toxicity, excluding:

- Grade 3 AST, ALT, and/or total bilirubin elevation for less than 7 days.
- Grade 3 neutropenia (without fever and not requiring growth factor support) for less than 7 days.
- Grade 3 thrombocytopenia without clinically significant bleeding.
- Grade 3 lymphopenia.
- First occurrence of Grade 3 electrolyte abnormalities and/or creatinine clearance decrease resolving to less than Grade 2 (or baseline if baseline is Grade 2 or above) within 48 hours with supportive treatment.
- Grade 3 fatigue, weakness, nausea, or other manageable constitutional symptom.
- Grade 3 vomiting or diarrhea that lasts for less than 48 hours with antiemetic or antidiarrheal medications.

Grade 4 hematologic or non-hematologic toxicity, excluding:

- First occurrence of Grade 4 electrolyte abnormalities resolving to less than Grade 2 (or baseline if baseline is Grade 2 or above) within 24 hours with supportive treatment.
- Grade 4 lymphopenia.
- Grade 4 manageable constitutional symptom.
- Grade 4 vomiting or diarrhea that lasts for less than 24 hours with antiemetic or antidiarrheal medications.

Any toxicity, regardless of the NCI CTCAE grade, resulting in discontinuation, dose reduction, or treatment with less than 75% of planned doses will be reviewed by the SRC and will be considered a DLT if the SRC determines the toxicity cannot be attributed to the patient's underlying disease, other medical condition, or concomitant medications.

AEs in the above categories that manifest after the DLT window (e.g., the first 28 days of treatment in C1) or other cumulative toxicities will be considered in the final definition of the MTD and/or the ultimate dose selected for further investigation.

For purposes of defining the MTD, patients will be evaluated according to the actual starting dose of selpercatinib on the first day of treatment. For most patients, this will be defined by the cohort to which they are assigned. Patients who receive at least 75% of the planned total dose in the first 28 days of treatment in C1 will be considered to have sufficient study drug exposure to be evaluated in support of dose escalation. Each patient who receives less than 75% of planned doses during C1 will be reviewed by the SRC. If the SRC determines that the reason(s) for treatment discontinuation is not related to the patient's underlying disease, other medical condition, or concomitant medications, the treatment discontinuation will be considered a DLT. Otherwise, the patient will be considered to have inadequate drug exposure and will be replaced for the determination of the MTD but will remain part of the safety population if they received at least one or more doses of study drug.

3.6 Phase 2

A dose of 160 mg BID has been selected by the SRC as the RP2D. Therefore, up to ~875 patients with advanced solid tumors with evidence of 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 six Phase 2 cohorts (Figure 3-1) as noted below to better characterize the safety and efficacy of selpercatinib in patients with specific abnormalities in RET. For all cohorts except Cohort 5, evidence of a *RET* gene alteration in tumor (i.e., not just blood) as defined in Table 3-3 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 (up to ~250 patients): *RET* fusion-positive solid tumor progressed on or intolerant to ≥ 1 prior standard first-line therapy (see Table 4-1 for standard first-line therapies)

- Cohort 2 (up to ~125 patients): *RET* fusion-positive solid tumor without prior standard first-line therapy (for countries and sites where approved; Germany and South Korea is excluded.)
- Cohort 3 (up to ~125 patients): *RET*-mutant MTC progressed on or intolerant to ≥ 1 prior standard first-line cabozantinib and/or vandetanib
- Cohort 4 (up to ~125 patients): *RET*-mutant MTC without prior standard first-line cabozantinib or vandetanib or other kinase inhibitors(s) with anti-RET activity (see Appendix A for examples, for countries and sites where approved; Germany and South Korea is excluded).
- Cohort 5 (up to ~200 patients):

  Cohorts 1-4 without measurable disease;

  MTC not meeting the requirements for Cohorts 3 or 4;

  MTC syndrome spectrum cancers (e.g., MTC, pheochromocytoma), cancers with neuroendocrine features/differentiation, or poorly differentiated thyroid cancers with other *RET* alteration/activation may be allowed with prior Sponsor approval;

  cfDNA positive for a *RET* gene alteration not known to be present in a tumor sample.
- Cohort 6 (up to ~50 patients): Patients who are otherwise eligible for Cohorts 1-5 who discontinued another RET inhibitor may be eligible with prior Sponsor approval.
- Cohort 7 (up to ~19 patients): Patients with a histologically confirmed stage IB-IIIA NSCLC and a RET fusion; determined to be medically operable and tumor deemed resectable by a thoracic surgical oncologist, without prior systemic treatment for NSCLC. This cohort was removed from study as of 01June2022. One patient from a site in the US was enrolled and has discontinued treatment.

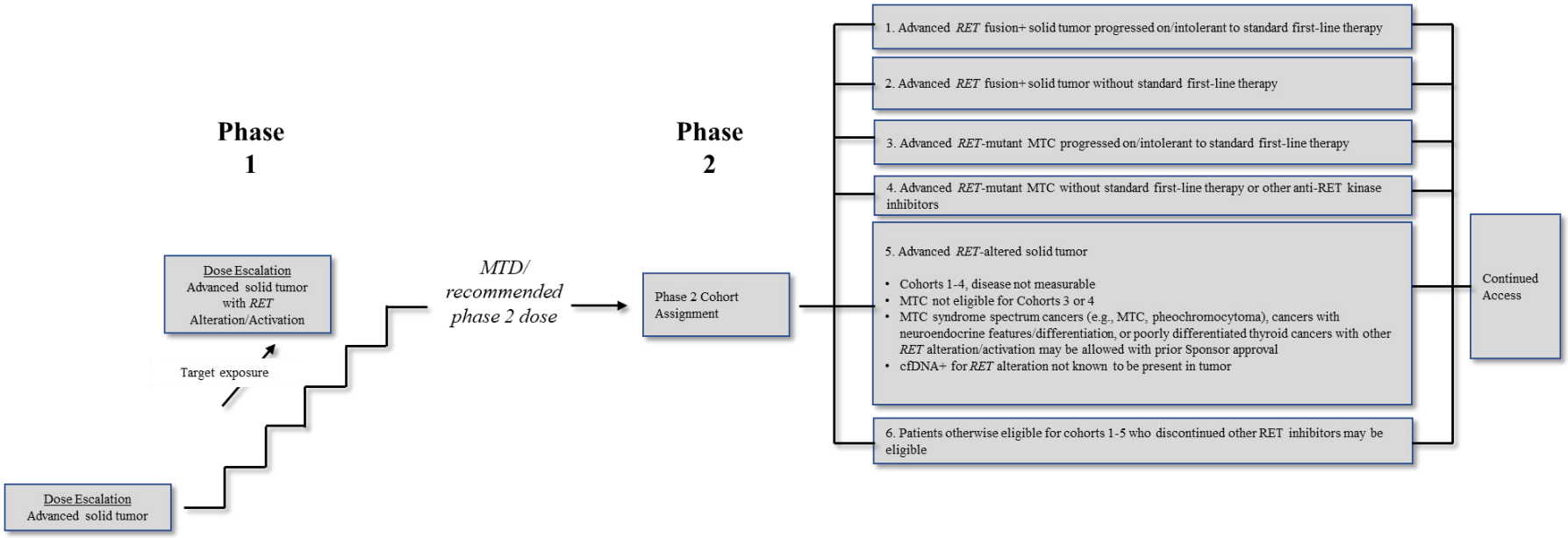
These patients will be treated at the MTD if one is identified or at a lower dose level (i.e., the recommended dose for further study) chosen by the SRC that has a DLT rate < 33%, is safe, and is likely to provide RET target engagement (i.e., the observed drug exposure in patients at that dose is associated with preliminary evidence of efficacy and is in agreement with the exposure-efficacy relationship predicted from preclinical data). In addition, the dose chosen for Phase 2 may be changed by the SRC based on emerging data (e.g., PK, safety, and/or efficacy), as long as the new dose is not greater than the highest dose that has a DLT < 33% and is determined to be safe by the SRC in Phase 1. If the RP2D is changed, patients enrolled to Phase 2 at a different dose may have the dose changed to the new dose.

Selpercatinib will be administered in oral form at the dose determined during dose escalation (MTD or recommended dose for further study). Each cycle will consist of either 28 days or 84 days, depending on the patient's duration on treatment (see Section 7). Patients treated during Phase 1 at the dose chosen for further study and who also meet the criteria for one of the Phase 2 cohorts may be considered as part of the evaluable patients for that cohort.

The study drug schedule and treatment assessments for Phase 2 are described in Section 6.2.3 and Table 7-1, respectively.

A statistical justification for cohort size is discussed in Section 8.3.

Figure 3-1 Study Schema



Abbreviations: cfDNA = circulating free tumor DNA; MTC = medullary thyroid cancer; MTD = maximum tolerated dose.

3.6.1 Rationale for the Starting Dose of 160 mg BID for Phase 2

In this study (LOXO-RET-17001 [J2G-OX-JZJA]), patients were enrolled in a dose escalation design that proceeded through the proposed dose levels until the SRC and the Sponsor determined that a suitable dose was achieved based on the available data (safety, PK exposure, clinical activity).

Following the completion of the DLT period for the 160 mg BID dose, 3 patients were DLT-evaluable and 1 patient was not DLT-evaluable (due to missed doses secondary to unrelated hypertension). There were no significant AEs, laboratory or other abnormalities reported for the 3 patients. Therefore, the SRC recommended to open the next dose escalation cohort at a dose of 240 mg BID while continuing to enroll patients at 160 mg BID ("backfill"). At a dose of 240 mg BID, 2 of 6 patients experienced DLTs: Grade 3 tumor lysis syndrome and Grade 3 thrombocytopenia (refer to IB Section 5.5.1.3). Based on the cumulative PK, safety and efficacy data for all patients enrolled to date at doses of 20 mg QD through 240 mg BID mg BID (n=89), which included a total of 24 patients treated at a dose of 160 mg BID (4 during dose escalation and 20 during backfill), the SRC selected 160 mg BID as the RP2D while recommending continued dose exploration at a dose of 200 mg BID. Three patients were treated at this dose without DLTs.

In summary, a dose of 160 mg BID was selected as the RP2D after careful and slow dose escalation; and based on the cumulative PK, safety and efficacy data for a meaningful number of patients treated at multiple doses. Although the clinical experience with patients ages 12 to 17 years is limited to date, selpercatinib exposure is not expected to be significantly different for patients in this age group than from older patients. The Sponsor has implemented a careful and robust safety monitoring plan as part of the protocol that consists of regular clinic visits and evaluations and frequent monitoring of laboratory values and electrocardiograms (ECGs).

3.7 Definition of RET Alterations

The specific *RET* gene alterations required for enrollment to Cohorts 1-4 during Phase 2 are defined in Table 3-3 and Appendix B (Table 11-2). *RET* mutations and fusions will be identified from a laboratory with CLIA, ISO/IEC, CAP, or similar certification as per local guidelines including but not limited to IVDR compliance as applicable, so long as a written Molecular Pathology Report is available and clearly asserts the presence of the referenced *RET* alteration.

Table 3-3 Definition of RET Alterations

RET* mutation
Previously reported activating *RET* gene mutation excluding synonymous, frameshift, or nonsense mutations. See Appendix B (Table 11-2) for examples. For MTC, *RET* gene mutation not known to be activating, negative, or unknown may be enrolled during Phase 1, and with Sponsor approval, to Cohort 5 of Phase 2.
RET* fusion
By PCR or NGS (FISH as the only molecular result is acceptable for Phase 1 dose escalation and Cohort 5 but not Cohorts 1 and 2 of Phase 2 [dose expansion]).

Abbreviations: CAP = College of American Pathologists; CLIA = Clinical Laboratory Improvement Amendments; FISH = Fluorescence in Situ Hybridization; ISO/IEC = International Organization for Standardization/Independent Ethics Committee; MTC = medullary thyroid cancer; NGS = next generation sequencing; PCR = polymerase chain reaction.

* According to laboratory with CLIA, ISO/IEC, CAP, or similar certification as per local guidelines including but not limited to IVDR compliance as applicable, so long as a written Molecular Pathology Report is available and clearly asserts the presence of the referenced *RET* alteration.

3.8 Number of Patients

During Phase 1, it is anticipated that approximately 30 patients (up to 6 patients per dose cohort) will be required to be enrolled in order to define the MTD (or RP2D) of selpercatinib. The actual number of patients enrolled is dependent on the number of patients enrolled in each dose escalation cohort, the number of cohorts enrolled, and when DLTs occur (if they occur). The safety of the patients enrolled is ensured with careful monitoring and rules for escalation so that an excessive number of patients are not unnecessarily exposed to a dose level that exceeds the MTD. Allowing intra-patient dose escalation (provided that the patient is tolerating their current dose and the dose level to which the patient will be escalated has already been evaluated, has a DLT rate of < 33%, and has been declared safe by the SRC) can minimize the chances that patients are exposed to a sub-therapeutic dose. Selected dose levels previously declared safe by the SRC may be expanded during Phase 1 to include a total of approximately 15 patients to further investigate the tolerability, PK, and biological activity of selpercatinib. If approximately 15 patients are enrolled in each planned dose level (levels 1-8), a total of approximately 120 patients will be enrolled in Phase 1.

During Phase 2, up to ~875 patients will be enrolled.

Refer to Section 8.3 for the statistical justification of initial sample/cohort size.

3.9 Investigational Sites

Approximately 50 to 100 institutions will be recruited to enroll patients.

4. SELECTION OF STUDY POPULATION

Potential patients age 18 years and older must sign an informed consent form (ICF) before any study-specific screening tests may be conducted.

Potential patients younger than age 18 years will require an assent according to local rules and regulations in addition to an informed consent signed by a parent or legal guardian. Screening tests are described in Section 7.1.

4.1 Inclusion Criteria for Phase 1

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. 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. A *RET* gene alteration is not required initially. Once adequate PK exposure is achieved (see below), evidence of *RET* gene alteration in tumor and/or blood is required (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 CLIA, ISO/IEC, CAP or other similar certification as per local guidelines including but not limited to IVDR compliance as applicable. The Sponsor should be contacted to discuss test results from labs where such certification is not clearly demonstrated to determine eligibility.

    Notes:

    - During Phase 1, a RET gene alteration is not required initially. The Sponsor's preclinical data indicates that a selpercatinib plasma level of 70 ng/mL is equivalent to the IC50 for RET (corrected for human plasma protein binding). Therefore, once a dose level is achieved that: (1) is associated with a DLT rate of < 33%; (2) is deemed safe by the SRC; and (3) is associated with a Cmin of > 70 ng/mL at steady state in ≥ 70% of patients in the same dosing cohort (e.g., 3/3, 3/4, 4/5, 5/6 patients, etc.), enrollment to subsequent dose levels during Phase 1 will be restricted to patients with: (1) RET fusion-positive solid tumors; (2) MTC; (3) an advanced solid tumor that harbors a RET gene alteration (excluding synonymous, frameshift, or nonsense mutations); or (4) with prior Sponsor approval, an advanced solid tumor with other evidence of RET activation.
    - A positive germline test for a *RET* mutation is acceptable for patients with MTC.

- Local testing in a CLIA, ISO/IEC, CAP, or other similar certified laboratory as per local guidelines including but not limited to IVDR compliance as applicable, is sufficient.
- In all cases, an anonymized/redacted Molecular Pathology Report or other report(s) describing tumor *RET* (and other) alteration analysis should be submitted to the Sponsor or designee during/prior to eligibility.

4. Measurable or non-measurable disease as determined by RECIST 1.1 or RANO as appropriate to tumor type.
5. At least 18 years of age.
    - For countries and sites where approved, patients as young as 12 years of age may be enrolled. (Canada, South Korea, and Germany are excluded from enrolling minors [patients under 18 years of age] into the study).
6. Eastern Cooperative Oncology Group (ECOG) performance status score of 0, 1, or 2 (age ≥ 16 years) or Lansky Performance Score (LPS) ≥ 40% (age < 16 years) 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.

    Notes:
    - Patients who do not have adequate archival tumor tissue available (refer to specific archival tissue requirements in Section 7.8.5.1) should undergo a fresh tumor biopsy, if it is considered safe to perform, prior to treatment (requirement may be waived with Sponsor approval).
    - 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) ≥ 1.0×10^9/L not requiring growth factor support for at least 7 days prior to treatment, and
    - Platelet count ≥ 75×10^9/L not requiring transfusion support for at least 7 days prior to treatment, and
    - Hb ≥ 9 g/dL not requiring transfusion support or erythropoietin for at least 7 days prior to treatment.
10. Adequate hepatic function, defined as:

    ALT and 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 ≥ 30 mL/minute (up to 6 patients with an estimated glomerular filtration rate [eGFR]) ≥ 15 and < 30 mL/minute will be allowed to enroll with Sponsor approval).
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 1 month following the last dose of study treatment.

    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
            - 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 treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.
    - 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.

Women of childbearing potential is a woman who is fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.

A man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy.

4.2 Inclusion Criteria for Phase 2

Inclusion Criteria are the same as for Phase 1, with the following modifications:

1. Cohorts 1 and 3: failed or intolerant to standard of care; Cohorts 2 and 4: without prior standard-first line therapy. See Table 4-1 for examples.

Table 4-1 Standard of Care Therapies for Cohorts 1-4

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 and/or lenvatinib, 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* Fusion-Positive Solid Tumor	Without prior standard-first line therapy, only if Inclusion Criteria 1 from Phase 1 is met: no standard therapy exists, or in the opinion of the Investigator is not a candidate for or would be unlikely to tolerate or derive significant clinical benefit from standard therapy, or decline standard therapy
Cohort 3: *RET*-mutant MTC	Cabozantinib or vandetanib or both agents
Cohort 4: *RET*-mutant MTC	Without prior standard-first line therapy, only if Inclusion Criteria 1 from Phase 1 is met: no standard therapy exists, or in the opinion of the Investigator is not a candidate for or would be unlikely to tolerate or derive significant clinical benefit from standard therapy, or decline standard therapy

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 = program death-ligand 1; VEGF = vascular endothelial growth factor.
Note: Standard of Care may vary by country

2. Cohorts 1-4: enrollment will be restricted to patients with evidence of a *RET* gene alteration in tumor (i.e., not just blood) as defined in Table 3-3. However, a positive

germline DNA test for a *RET* gene mutation as defined in Table 3-3 is acceptable in the absence of tumor tissue testing for patients with MTC.

3. Cohorts 1-4: at least one measurable lesion as defined by RECIST 1.1 or RANO, as appropriate to tumor type and not previously irradiated (unless PD for the irradiated lesion[s] has been radiographically documented).

4. Cohort 4: radiographic PD within the previous 14 months.

   Note: Patients otherwise eligible for Cohort 4 who do not demonstrate radiographic PD within the previous 14 months may be enrolled to Cohort 5 if a compelling rationale is provided by the investigator and approved by the Sponsor.

5. Cohort 6: patients otherwise eligible for Cohorts 1-5 who discontinued another selective RET inhibitor(s) may be eligible with prior Sponsor approval.

   Note:

   Examples of RET inhibitors may include TPX0046, pralsetinib (BLU-667), or BOS172739.

6. Cohort 5: Patients who otherwise are eligible for:

   - Cohorts 1-4 without measurable disease;
   - MTC not meeting the requirements for Cohorts 3 or 4;
   - MTC syndrome spectrum cancers (e.g., MTC, pheochromocytoma), cancers with neuroendocrine features/differentiation, or poorly differentiated thyroid cancers with other *RET* alteration/activation may be allowed with prior Sponsor approval;
   - cfDNA positive for a RET gene alteration not known to be present in a tumor sample.

7. Criterion 7 is removed.

4.3 Exclusion Criteria for Phase 1 and Phase 2

Patients meeting any of the following criteria are to be excluded from study participation:

1. Phase 2 Cohorts 1-4: an additional validated oncogenic driver that could cause resistance to selpercatinib treatment. See Appendix C (Table 11-3) for examples.

2. Cohorts 1-5: prior treatment with a selective RET inhibitor(s) (including investigational selective RET inhibitor[s]).

   Notes:

   Patients otherwise eligible for Cohorts 1-5 who discontinued another selective RET inhibitor may be eligible for Phase 2 Cohort 6 with prior Sponsor approval.

3. Investigational agent or anticancer therapy (including chemotherapy, biologic therapy, immunotherapy, anticancer Chinese medicine or other anticancer herbal remedy) 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. Refer to Section 6.3.2 for allowable concurrent therapies.

   Note: Potential exception for this exclusion criterion will require a valid scientific justification and approval from the Sponsor.

4. Major surgery (excluding placement of vascular access) within 2 weeks prior to planned start of selpercatinib.

5. 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.

6. Any unresolved toxicities from prior therapy greater than CTCAE Grade 1 at the time of starting study treatment with the exception of alopecia and Grade 2, prior platinum-therapy related neuropathy.

7. Symptomatic primary CNS tumor, 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: During the Phase 2 portion of the study, 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.

8. 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) interval > 470 msec during Screening. Correction of suspected drug-induced QTcF prolongation may be attempted at the Investigator's discretion if clinically safe to do so.

   Notes:

   - Patients with implanted pacemakers may enter the study without meeting QTc criteria due to nonevaluable measurement if it is possible to monitor for QT changes.

- Patients with bundle branch block may be considered for study entry if QTc is appropriate by a formula other than Fridericia's and if it is possible to monitor for QT changes.

9. 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.
10. Clinically significant active malabsorption syndrome or other condition likely to affect gastrointestinal absorption of the study drug.
11. Uncontrolled symptomatic hyperthyroidism or hypothyroidism.
12. Uncontrolled symptomatic hypercalcemia or hypocalcemia.
13. Pregnancy or lactation.
14. Active second malignancy other than minor treatment of indolent cancers.
15. History of hypersensitivity to any of the study drug capsule components, or any of the liquid suspension components (for patients that cannot swallow capsules).

5. ENROLLMENT PROCEDURES

For all patients, a copy of the anonymized/redacted Molecular Pathology Report, or other report(s) describing tumor *RET* (and/or other) mutation analysis should be submitted to the Sponsor or designee during Screening for review prior to patient enrollment. As part of pre-screening, it is advised to provide this upon patient identification for the study. If a patient does not have a prior Molecular Pathology Report or other report and is being considered for enrollment during the initial part of Phase 1 when a *RET* gene alteration is not required, this requirement may be waived with prior Sponsor approval.

A representative from the investigational site will contact the Sponsor or designee when a potential study candidate is identified and a patient number (which will consist of a 3-digit site number followed by a sequential accession number) will be assigned that will be used throughout both Screening and study participation. Once screening procedures have been completed for the patient, a completed enrollment form will be submitted to the Sponsor or designee in order to confirm eligibility.

Patients who are determined to be screen failures can be re-screened. Re-screened patients will be provided a new patient number.

The enrollment form will be returned to the site with the cohort assignment (if applicable) and must be received by the site before treatment may commence. Refer to the Study Manual for enrollment form, contact numbers, and other details of enrollment.

6. TREATMENT

6.1 Investigational Product

Selpercatinib 30% simple blend is provided in 40-mg capsules that will be made available to the sites in bottles of 60 capsules/bottle, and 80-mg capsules that will be provided to the sites in bottles of 120 capsules/bottle. The site pharmacist will dispense capsules or bottles (as permitted by the site) 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 BSA-based).

Capsules are to be stored at controlled room temperature (between 15° C and 30° C).

Intervention Name [a]	Selpercatinib
Authorized as defined by EU Clinical Trial Regulation	Authorized and not used according to EU authorization

[a] Study intervention is defined as any medicinal product(s) or medical device(s) intended to be administered to or used by a study participant according to the study protocol.

Additional details regarding the investigational product and instructions for dissolving capsules are provided in the selpercatinib Pharmacy Manual and the selpercatinib IB.

Under extenuating circumstances (e.g., personal emergencies, natural disasters, civil unrest, etc.), and where allowed by regional regulatory authorities, IP shipment direct from site to patient is permitted on case-by-case basis and with sponsor approval.

Packaging and labeling

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

6.2 Selpercatinib Administration

6.2.1 General Dosing Instructions

Dosing for an individual should be at a consistent time each day and BID dosing will be separated by approximately 12 hours (a minimum of 6 hours between consecutive doses). Selpercatinib may be given with or without food, but should be taken in a consistent fashion.

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.

6.2.2 Cycle 1: Phase 1 and Phase 2

Patients will begin dosing on C1D1 according to their assigned cohort. Serial blood samples for PK monitoring will be collected and the patient will be monitored for safety as outlined in Section 7.2. Cycle length is 28 days during both Phase 1 and Phase 2; the DLT treatment/observation period during Phase 1 will consist of Days 1-28 of C1.

6.2.3 Cycles 2 and Higher: Phase 1 and Phase 2

In accordance with the assigned dose level (or for Phase 2, the RP2D), each patient will receive selpercatinib QD or 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.

6.2.4 Dose Delays/Modifications

Cycles are 28 days in duration regardless of dose interruption unless the dose interruption includes D1 of the next cycle in which case the next cycle will start with resumption of study drug. In this situation, disease assessments should continue to follow the original schedule.

For Phase 1 and Phase 2, 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.

Dose Delays/Modifications for Specific Adverse Events

Safety and dose modification guidance is provided below for hypersensitivity, LFT abnormalities, thrombocytopenia, hypertension, hemorrhage, and dry mouth. Additional safety guidance is provided in Section 6 of the selpercatinib IB.

Hypersensitivity

Drug hypersensitivity reactions to selpercatinib have been reported. Patients developed a constellation of symptoms and findings characterized by a maculopapular rash, often preceded by fever, with associated arthralgias or myalgias during the patient's initial weeks of treatment, which were then followed by at least one of the following:

- more commonly: platelet decrease and AST/ALT increase
- less commonly: blood pressure decrease, tachycardia, and creatinine increase

If selpercatinib drug hypersensitivity is suspected, study drug should be held and treatment with steroids at 1 mg/kg prednisone (or equivalent) may be initiated at investigator discretion. Upon resolution, selpercatinib may be resumed at a reduced dose of 40 mg BID while continuing

steroids at the same dose. Hypersensitivity has recurred in some patients, typically at 3-6 hours following drug administration. If recurrence is severe, selpercatinib should again be held; patients with mild recurrence (e.g., isolated instances of rash or myalgias or low-grade fever) have been able to cautiously continue treatment with supportive therapy (e.g., topical treatments, ibuprofen).

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. 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.

Liver Function Test Abnormalities

LFT laboratory testing (AST, ALT, total and direct bilirubin, ALP) should be performed every 2 weeks through C4D1 and then D1 of every subsequent treatment cycle. If a patient experiences ≥ Grade 3 elevated LFT increases, study drug should be held and evaluation for potential alternative causes should be conducted (e.g., history of other hepatotoxic medications/ substances, viral serologies, liver imaging). LFTs should be monitored at least weekly until resolution to normal/baseline (depending on the clinical situation, resolution to Grade 1 if baseline is normal may be acceptable but awaiting normalization is preferable). If the 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. Some but not all patients were previously treated with immune checkpoint inhibitors (ICIs), and increased hepatotoxicity has been previously associated with sequential ICI therapy and TKIs in NSCLC (Lin et al, 2018). Therefore, prior ICIs may be a potential contributing factor in these patients; for some, concomitant treatment with steroids correlated with improvement in persistent LFT abnormalities. Therefore, in patients in whom there is thought to be an immune component to the LFT abnormalities observed, i.e., prior ICI exposure or liver biopsy results demonstrating an immune infiltrate, treatment with steroids may be added to the dose interruption recommendations below.

Upon resolution, for patients who received 160 mg BID, selpercatinib may be resumed at a reduced dose of 80 mg BID with weekly LFT monitoring. In the absence of recurrent LFT abnormalities, the dose of selpercatinib may be escalated sequentially to 120 mg BID after a minimum of 2 weeks at 80 mg BID, and again to 160 mg BID, and after a minimum of 4 weeks at 120 mg BID. 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 LFT monitoring may be decreased (e.g., additional midcycle evaluation for 2 cycles and then at the start of every cycle thereafter). For patients who experience ≥ Grade 3 elevated LFTs on a different dose than 160 mg BID, the dose should be reduced by 2 dose levels with subsequent re-escalation and monitoring as noted above upon resolution. If the patient experiences ≥ Grade 3 elevated LFTs at a dose of 40 mg BID, selpercatinib should be discontinued.

Thrombocytopenia

A complete blood count (CBC) should be performed during Screening, C1D1, C1D15 and Day 1 of every subsequent cycle. If a patient is discovered to have thrombocytopenia ≥ Grade 3, study drug should be held and the patient should be evaluated for alternative causes (medications/substances, viral studies). A hematology consultation may be considered as necessary to understand the etiology and to consider a role for concomitant steroid therapy. The patient should undergo weekly CBC testing until the event has recovered to normal/baseline. Upon recovery, the patient should resume selpercatinib at a reduced dose (e.g., 120 mg BID or 80 mg BID) with weekly CBC surveillance for 1 full cycle.

Hypertension

All Investigators should optimize patients' blood pressure to an ideal reading of ≤ 140/90 mmHg (if necessary) prior to initiation of study drug. If hypertension, defined as a sustained increase in blood pressure from baseline on ≥ 2 readings on ≥ 2 separate occasions, or a clinically significant elevation requiring acute treatment, occurs, study drug may be interrupted at the discretion of the Investigator while considering initiation of a new anti-hypertensive medication regimen, or alteration of a preexisting regimen is optimized to improve BP control; ideally 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 (i.e., rechallenge is allowable with adequate management of hypertension). 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 BP control has been obtained; with clinically appropriate monitoring to ensure elevated BP does not recur. If the patient experiences uncontrolled ≥ Grade 3 hypertension despite anti-hypertensive regimen optimization and study drug dose reduction to 40 mg BID, selpercatinib should be discontinued.

Hemorrhage

Rare patients have reported serious hemorrhagic AEs related to study drug. The majority of hemorrhagic events have been Grade 1-2 and non-serious in nature. Clinical signs and symptoms of bruising and bleeding should be monitored while patients are on selpercatinib. For patients who develop an AE ≥ Grade 3, selpercatinib should be held until the event resolves to ≤ Grade 1 (or baseline) and patients with severe or life-threatening hemorrhagic events should discontinue selpercatinib therapy.

Dry Mouth

Dry mouth (xerostomia) occurs in about 42% of patients in this study, and 37% were deemed by Investigators as related to selpercatinib. Although these events have been Grades 1-2, prolonged and inadequately managed dry mouth can lead to severe xerostomia and tooth carries resulting in tooth extractions. Clinical signs and symptoms of dry mouth should be monitored while patients are on selpercatinib. Management can include oral rinses or other medication that stimulates saliva production, such as pilocarpine- or cevimeline-containing agents, and dose reductions.

Interstitial Lung Disease/Pneumonitis

For Grade 2, hold dosing until resolution. Resume at next lower dose level. Discontinue selpercatinib for recurrent interstitial lung disease/pneumonitis. For Grade 3 or 4, discontinue selpercatinib.

Chylothorax and Chylous Ascites

If a patient develops a pleural effusion or abdominal ascites or both while on selpercatinib, fluid sampling and testing should be considered as part of the management algorithm whenever possible. The etiology of this finding varies and distinguishing chylous fluid from malignant (as well as other causes such as infectious) may impact management significantly (for example, presumption of disease progression with premature discontinuation of therapy). Additionally, a diagnosis of chylous effusions or ascites or both may indicate a role for conservative measures such as fluid replacement, dietary alteration, or medical therapy or both (for example, somatostatin analogue) prior to consideration of more invasive measures.

Selpercatinib interruption and dose modification should follow the general strategy based upon severity of the event.

<u>Phase 1, Cycle 1</u>

Dose reductions are permitted but will be considered a DLT if the dose was reduced for a toxicity(ies) that cannot be reasonably attributed to the patient's underlying disease, other medical condition or concomitant medications.

A patient who experiences a DLT may have selpercatinib dosing held for up to 28 days to allow for recovery (to Grade 1 or less or baseline if baseline is Grade 2 or above).

The patient may restart therapy if it is considered in his/her best interest to continue therapy. Upon restarting, the patient may have the dose reduced by one dose level (Table 6-1). If the patient requires a dose delay of > 28 days, the patient will have treatment permanently discontinued unless there is a compelling clinical rationale for additional dose reduction(s) articulated by the Investigator and approved by the Sponsor. For each patient, a maximum of 2 dose reductions will be allowed, unless there is a compelling clinical rationale for additional dose reduction(s) articulated by the Investigator and approved by the Sponsor.

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

Phase 1 Cycle 2 and Beyond, and Phase 2

A patient who experiences a clinically significant AE (i.e., greater than Grade 2 or more than 1 grade change from baseline if baseline is Grade 2 or above) may have selpercatinib dosing held for up to 28 days to evaluate the AE and to allow for recovery (to Grade 1 or baseline level).

Upon recovery, the patient may restart therapy if it is considered in his/her best interest to continue therapy. Upon restarting, the patient may have the dose reduced by at least one dose level (Table 6-1). If the AE does not recover to Grade 1 or less within 28 days (or baseline), the patient will have treatment permanently discontinued, unless there is a compelling clinical rationale for additional dose reduction(s) articulated by the Investigator and approved by the Sponsor. For each patient, a maximum of 2 dose reductions will be allowed, unless there is a compelling clinical rationale for additional dose reduction(s) articulated by the Investigator and approved by the Sponsor (Table 6-1).

Table 6-1 Suggested Toxicity Management

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 event; BID = twice daily; LFT = liver function test.
*For some AEs (e.g., hypersensitivity reactions and LFT increases), an alternative re-escalation strategy should be followed, which includes a dose reduction to 40 mg BID and alternative dosing at 60 mg BID. Occurrence of these AEs as well as implementation of the mentioned dosing should be discussed with the Sponsor. Additional information is provided in Section 6 of the selpercatinib IB, Summary of Data and Guidance for the Investigator.

Patients who have been dose reduced and who tolerate selpercatinib without toxicity for at least one cycle may be re-escalated to their previous dose level with the agreement of the Investigator

and the Sponsor. Some AEs (e.g., hypersensitivity reactions and LFT increases) have an alternative re-escalation strategy. For additional information, refer to Section 6 of the selpercatinib IB, Summary of Data and Guidance for the Investigator.

All dose interruptions and dose modifications and the reasons for those changes will be recorded in the eCRF.

6.3 Prior and 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, nutritional supplements, vaccinations, and other remedies. Additional prior excluded medications are indicated in the Exclusion Criteria (Section 4.3).

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 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; systemic glucocorticoids (approximately 10 mg per day prednisone or equivalent, unless there is a compelling clinical rationale for a higher dose articulated by the Investigator and approved by the Sponsor; no dose restriction for administration routes other than IV or oral), including short courses to treat asthma, chronic obstructive pulmonary disease, etc.; 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 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 of tumor sites or target lesions 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 2-3 days) before and after radiation therapy or surgery. Any concern for disease flare due to a prolonged period off of selpercatinib should be discussed with the Sponsor, who may permit holding selpercatinib for a shorter period of time.

6.3.3 Restricted Concomitant Medications

Avoid concomitant use of strong and moderate CYP3A inhibitors (refer to Appendix D) with selpercatinib which increase selpercatinib plasma concentrations, which may increase the risk of selpercatinib adverse reactions, including QTc interval prolongation. 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 (refer to the selpercatinib IB).

Avoid coadministration of strong or moderate CYP3A inducers (refer to Appendix D) with selpercatinib which decrease selpercatinib plasma concentrations. 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.

Avoid concomitant use of a PPI, H2 receptor antagonists, or locally acting antacids with selpercatinib. If concomitant use cannot be avoided, the following guidance should be adhered to:

- Take selpercatinib with food when co-administered with a PPI.
- Take selpercatinib 2 hours before (± 30 minutes) or 10 hours after (± 30 minutes) administration of an H2 receptor antagonist.
- Take selpercatinib 2 hours before (± 30 minutes) or 2 hours after (± 30 minutes) administration of a locally-acting antacid.

Examples of PPIs are omeprazole (Prilosec®), esomeprazole (Nexium®), lansoprazole (Prevacid®), pantoprazole (Protonix®), rabeprazole (Aciphex®), and dexlansoprazole (Dexilant®) (refer to Appendix E). Examples of H2 blocking agents are ranitidine (Zantac®), famotidine (Pepcid®), and cimetidine (Tagamet®). Examples of antacids are aluminum hydroxide/magnesium hydroxide/simethicone (Maalox®), and calcium carbonate (TUMS®).

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).

Coadministration of medications known to prolong QTc should be avoided if possible (refer to Appendix J for examples).

In addition, except as indicated in Section 6.3.2, patients are not allowed to receive concomitant systemic anti-cancer agents, hematopoietic growth factors for prophylaxis in C1, therapeutic monoclonal antibodies, drugs with immunosuppressant properties, medications, 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.

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.

6.3.5 Transporter Interactions

Selpercatinib is a substrate for the drug transporters P-gp and BCRP and in principle inhibitors of these transporters would lead to increased oral absorption of selpercatinib. However, inhibitors of these transporters are not prohibited because interim results of a clinical study of selpercatinib show that absolute bioavailability of selpercatinib is approximately 74%, thus there is little potential for increased absorption because bioavailability cannot go over 100%. In vitro, selpercatinib is a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP), but is not a substrate for OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, MATE1, or MATE2-K. In a clinical study, the PK of selpercatinib was not affected significantly by a P-gp inhibitor.

6.3.6 Effect of Selpercatinib on the PK of other Drugs

Avoid coadministration of selpercatinib with CYP2C8 and CYP3A substrates which may increase their plasma concentrations, which may increase the risk of adverse reactions related to these substrates and lead to increased adverse reactions. If coadministration cannot be avoided, follow recommendations for CYP2C8 and CYP3A substrates provided in their approved product labeling, and monitor patients for increased adverse reactions of these drugs.

Additional information regarding coadministration of selpercatinib with sensitive CYP2C8 substrates, sensitive CYP3A4 substrates, and other CYP450 Substrates is provided in the selpercatinib IB.

6.4 Removal of Patients from Therapy or Assessment

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 (see Section 7.7). 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. Sponsor approval is not required for continuing selpercatinib treatment upon a subsequent progression, provided that continued benefit to the patient is documented.
- 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
- Loss to follow-up
- Death
- Study terminated by Sponsor

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 7.5. Patients will enter LTFU where they may be required to undergo disease assessments (see Section 7.7).

6.5 Reasons for End of Study

Reasons for end of study could be:

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

A clinical trial is to be discontinued or terminated in case of an unacceptable risk, any relevant toxicity, or a negative change in the risk/benefit assessment. This might include the occurrence of AEs which character, severity or frequency is new in comparison to the existing risk profile. In addition, any data deriving from other clinical trials or toxicological studies which negatively influence the risk/benefit assessment might cause discontinuation or termination of the study.

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.

Routine laboratories, for example serum chemistries, hematology, and urinalysis, may be performed locally. Special assessments, such as PK and correlative studies, may be performed centrally or as individually indicated. 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. Additional information regarding handling and processing of these special samples is provided in the separate Laboratory Manual.

Patients who are tolerating selpercatinib may have a reduced in-clinic visit assessment schedule after 6 months on treatment as described in Table 7-1. From Cycle 7 and onward, patients will be required to return to the clinic for in-person visits only during cycles where radiographic disease assessments are required, and for EOT and SFU visits. During non-disease assessment cycles, patients may continue to return for in person visits or may opt to have routine laboratory tests (e.g., serum chemistries, hematology, and liver function tests) completed at local healthcare facilities in conjunction with a telemedicine visit (telephone or equivalent). During the remote assessment, the site will perform an ECOG assessment, an AE assessment including whether the patient is experiencing any new, or changes to existing, AEs/SAEs and concomitant medications, and will confirm study drug compliance and record missed doses. Patient responses during telemedicine visits will be recorded in source documents and results from any local assessments must be provided to the site for data entry into EDC. Patients who are on selpercatinib treatment for at least 2 years will be required to return to the clinic for in-person visits only during cycles where radiographic disease assessments are required, and for EOT and SFU visits. Routine laboratory tests and telemedicine visits are not required but should be performed as clinically indicated during non-disease assessment cycles.

Should telemedicine visits result in patient complaint or concern from the study Investigator, the patient should return to the study site or be seen by a local provider for further assessment(s).

Beyond Cycle 7, physical examination, and vital signs are not required during local, non-disease assessment cycles, but should be collected when the patient returns to the clinic for disease assessment cycles.

Table 7-1 Schedule of Assessments

Visit Window	Screening	Cycle 1				Cycle 2-6	Cycle 7-higher [b]	Intra-patient Dose Escalation		EOT [c]	SFU [d]	LTFU [e]
	Day -28 to Day -1	D1 ±2 Days	D8 ±2 Days	D15 ±2 Days	D22 [a] ±2 Days	±3 Days	±7 Days	D1 ±3 Days	D8 ±3 Days			
Informed Consent	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									X		
Physical examination and ECOG or LPS [h]	X	X	X	X		D1 of C2-C6	±7 days of each radiologic disease assessment	X	X	X	X	
Vital signs [i]	X	X	X	X		D1 of C2-C6	±7 days of each radiologic disease assessment	X	X	X	X	
12-lead ECG[j]	X	X	X			D1 of C2-C6	D1 of odd cycles (C7, C9, C11, C13) and then every 12 weeks until C26. After C26, obtain as clinically indicated.	X	X	X	X [k]	
Urine or serum pregnancy test [l]	X	X				D1 of C2-C6	D1 of C7, 8, 9, etc.*			X	X	
Hematology [m]	X	X		X		D1 of C2-C6	D1 of C7, 8, 9, etc.*	X		X	X	
Serum chemistries [n]	X	X		X		D1 of C2-C6	D1 of C7, 8, 9, etc.*	X		X	X	
Liver function tests [o]	X	X		X		D1 of C2-C6 and C2D15 and C3D15	D1 of C7, 8, 9, etc.*		X	X	X	

Visit Window	Screening	Cycle 1				Cycle 2-6	Cycle 7-higher [b]	Intra-patient Dose Escalation		EOT [c]	SFU [d]	LTFU [e]
	Day -28 to Day -1	D1 ±2 Days	D8 ±2 Days	D15 ±2 Days	D22 [a] ±2 Days	±3 Days	±7 Days	D1 ±3 Days	D8 ±3 Days			
Thyroid panel [p]	X			X		C3D1 and then ±7 days of each radiologic disease assessment	±7 days of each radiologic disease assessment					
Urinalysis [q]	X			X		As clinically indicated	As clinically indicated.*			X	X	
Calcitonin, CEA (MTC only) [r]	X	X		X		C2D1 and then ±7 days of each radiologic disease assessment	±7 days of each radiologic disease assessment			X		
Thyroglobulin (non-MTC thyroid cancers only) [s]	X	X		X		C2D1 and then ±7 days of each radiologic disease assessment	±7 days of each radiologic disease assessment			X		
Serum cortisol, serum ACTH, 24-hour urine for free cortisol [t]	X	X		X		C2D1 and then ±7 days of each radiologic disease assessment	±7 days of each radiologic disease assessment			X		
Radiograph of knee[gg]	X					Every 6 months	Every 6 months					
Whole blood for cfDNA analysis [u]		X		X		C2D1				X		
Whole blood for genomic DNA	X											
Disease assessment [v]	X					Every 8 weeks (±7 days) starting with C3D1 through C13D1. Every 12 weeks (±7 days) thereafter.	Every 8 weeks (±7 days) through C13D1. Every 12 weeks (±7 days) thereafter.			X [w]		X
Confirmatory disease assessment [y]						At least 4 weeks post 1st PR	At least 4 weeks post 1st PR					

Visit Window	Screening Day -28 to Day -1	Cycle 1 D1 ±2 Days	Cycle 1 D8 ±2 Days	Cycle 1 D15 ±2 Days	Cycle 1 D22 [a] ±2 Days	Cycle 2-6 ±3 Days	Cycle 7-higher [b] ±7 Days	Intra-patient Dose Escalation D1 ±3 Days	Intra-patient Dose Escalation D8 ±3 Days	EOT [c]	SFU [d]	LTFU [e]
Telemedicine Visit [z]							In parallel with local visits on non-disease assessment timepoints*					
Blood sample for PK [aa]			X						X			
EORTC QLQ-C30 or PedsQL [bb]		X				±7 days of each radiologic disease assessment	±7 days of each radiologic disease assessment			X		
Selpercatinib administration		→	→	→	→	→	→	→	→	→		
Patient dosing diary		→	→	→	→	→	→	→	→	→		
Patient bowel diary (MTC only) [cc]		X	X	X	X	D1 of C2-C6	D1 of C7, 8, 9, etc.*			X		
Adverse events [dd]	→	→	→	→	→	→	→	→	→	→	→	
Concomitant medications [ee]	→	→	→	→	→	→	→	→	→	→	→	
Survival [ff]												X

Abbreviations (for Table 7-1 and Footnotes): ACTH = adrenocorticotropic hormone; AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; C = cycle; C1D1 = Cycle 1 Day 1; CEA = carcinoembryonic antigen; cfDNA = circulating free tumor deoxyribonucleic acid; CR = complete response; CT = computed tomography; D = day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EDC = electronic data capture; EORTC-QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EOT = End of Treatment; IB = Investigator's Brochure; IV = intravenous; LDH = lactate dehydrogenase; LFT = liver function test; LPS = Lansky Performance Score; LTFU = Long-Term Follow-Up; MTC = medullary thyroid cancer; MRI = magnetic resonance imaging; PD = progressive disease; PedsQL = Pediatric Quality of Life Inventory-Core Module; PK = pharmacokinetics; PR = partial response; Q12W = every 12 weeks; QTcF = QT interval corrected for heart rate (Fridericia's formula); RANO = Response Assessment in Neuro-Oncology; RBC = red blood cell; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; SFU = Safety Follow-Up; TSH = thyroid-stimulating hormone; T_3 = free triiodothyronine; T_4 = free thyroxine; ULN = upper limit of normal; WBC = white blood cell.

* For Cycle 7 and beyond, patients may have laboratories (e.g., serum chemistries, hematology, liver function tests, and urinalysis) completed at the study site or at local healthcare facilities during non-disease assessment cycles. As a result of this reduced in-clinic visit assessment schedule, the Sponsor understands that certain assessments (e.g., physical examination, vital signs) may not be obtainable during visits at local healthcare facilities. Beyond Cycle 7, these assessments are optional during local, non-disease assessment cycles, but should be collected when the patient returns to the clinic for disease assessment cycles. Patients who are on selpercatinib treatment for at least 2 years will be required to return to the clinic for in-person visits only during cycles where radiographic disease assessments are required, and for EOT and SFU visits. As a result, visit frequency is increased from 4 weeks to 12 weeks, in line with imaging assessment schedule. Cycle length will be increased from 28 days to 84 days (see Section 7.3 for additional details). Routine laboratory tests and telemedicine visits are not required but should be performed as clinically indicated during non-disease assessment cycles.
  a. Telephone contact for safety.
  b. For Cycle 7 and beyond, patients may attend clinic visits only during cycles where radiographic disease assessments are required (Cycle 7, 9, 11, 13, and then Q12W thereafter) if telemedicine visit can be completed along with locally obtained lab assessments.
  c. End of Treatment (EOT): +7 days of the last dose or the decision to terminate treatment.
  d. Safety Follow-Up (SFU): 28 days (+7 days) after final dose of study drug.
  e. Long-Term Follow-Up (LTFU): approximately every 3 months (±1 month) after the last dose of study drug.
  f. For all patients, anonymized/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 ~25 × 5 um unstained slides. 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. A tissue biopsy to show PD may be collected at the time of progression if it can be safely performed. If oligometastatic disease constituting progression is identified, but the patient is otherwise stable and will continue selpercatinib beyond progression, the patient may undergo an optional fresh tumor biopsy to evaluate tumor changes that may have resulted from treatment.
  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. Beyond Cycle 7, physical examination is only required when the patient returns to the clinic for disease assessment cycles.
  i. Systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature. Beyond Cycle 7, vital sign collection is only required when the patient returns to the clinic for disease assessment cycles.

j. Obtain a single pre-dose ECG during Screening and again on C1D1. If the C1D1 pre-dose QTcF > 470 msec (QTcF = QT (msec)/$RR^{1/3}$), where RR (msec) = 60*1000/BPM), the Sponsor should be notified *prior* to dosing to determine whether the patient remains eligible. On C1D8 and thereafter, perform a single ECG at 2 hours (± 10 minutes) post-selpercatinib dosing. On days of PK collection, the ECG should be timed prior to the PK sample being drawn. Dose patients in the clinic to ensure accuracy of timing. If any ECG demonstrates QTcF 481500 msec, perform an additional- ECG at 4 hours (± 10 minutes) post dosing. If any ECG demonstrates QTcF > 500 msec, repeat the ECG twice (triplicate in total) 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. Please refer to protocol Section 6.2.4. and/or the selpercatinib IB for comprehensive dose modification information. For intra-patient dose escalation, ECGs should be performed pre-dose (up to 4 hours predose-) on Day 1 of the patient's new dose, and 2 hours post-selpercatinib-dosing (±10 minutes) on Days 1 and 8 of the patient's new dose. For patients on treatment post cycle 26, ECG to be obtained as clinically indicated.
k. Repeat only if EOT reading showed treatment-emergent abnormalities.
l. For women of childbearing potential: Serum pregnancy test at Screening, serum or urine pregnancy test at Day 1 of every cycle, and at EOT and SFU (surgically sterilized females or those who have not experienced menses for at least 2 years are not required to be tested).
m. Hematology including hemoglobin, hematocrit, RBC count, WBC count with differential (neutrophils [count and percent] and lymphocytes, monocytes, eosinophils, basophils [percent]), and platelet count). For intra-patient dose escalation, if Day 1 of the new dose falls on the same day (±3 days) of a previous hematology assessment (e.g., Day 1 of C2 and beyond), it is not necessary to repeat. Patients found to have treatment-emergent hematologic toxicity of Grades 3 or 4 will be monitored at least weekly until resolution.
n. Serum chemistries (non-fasting), including BUN (urea where BUN not tested), total cholesterol, creatinine, glucose, LDH, , sodium, potassium, calcium, chloride, bicarbonate, magnesium, phosphorus, albumin, and total protein. For intra-patient dose escalation, if Day 1 of the new dose falls on the same day (±3 days) of a previous serum chemistry assessment (e.g., Day 1 of C2 and beyond), it is not necessary to repeat. Patients found to have treatment-emergent laboratory toxicity of Grades 3 or 4 will be monitored at least weekly until resolution.
o. LFTs, including ALT, AST, alkaline phosphatase, and total and direct bilirubin. For intra-patient dose escalation, if Day 1 of the new dose falls on the same day (±3 days) of a previous liver function assessment (e.g., Day 1 of C2 and beyond), it is not necessary to repeat. Patients found to have treatment-emergent laboratory toxicity of Grades 3 or 4 will be monitored at least weekly until resolution. Increased LFT monitoring should be conducted following dose resumption and any dose re-escalation after toxicity (refer to Section 6 of the selpercatinib IB, Summary of Data and Guidance for the Investigator).
p. Thyroid-stimulating hormone (TSH), free triiodothyronine (T_3), and free thyroxine (T_4).
q. Complete urinalysis, including color, appearance, specific gravity, pH, glucose, ketones, occult blood, protein, leukocytes, nitrites. Beyond Cycle C1D15, urinalysis is only required if clinically indicated.
r. 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.
s. 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.
t. Optional for patients with Cushing's disease related to their cancer. If performed, urine collection should begin pre-dose.
u. Whole blood for cfDNA analysis should be obtained at C1D1 (pre-dose), C1D15 and C2D1. Whole blood for cfDNA analysis should be obtained at the EOT visit, even if radiologic disease assessment is not performed. If oligometastatic disease constituting progression is identified, but the patient is otherwise stable and will continue selpercatinib beyond progression, patients should have blood collected for cfDNA analysis.

v. Baseline disease assessment with radiographic tumor measurements using CT or MRI of chest, abdomen, and pelvis or any other areas with suspected disease involvement within 28 days of C1D1. During Phase 2, 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). For each modality, IV and oral contrast should be utilized (chest CT does not require IV contrast) 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) for one year 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 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 1.1 (or RANO, as appropriate to tumor type), if consistent with local regulatory authority requirements. In addition, an initial post baseline assessment on C2D1 (±7 days) is encouraged if consistent with regulatory guidelines. If a scan is performed on C2D1, the next scan should continue according to the schedule above (beginning at C3D1). All scans will be collected and stored at a central facility to permit central reviewer assessment if desired. Please see the Site Imaging Manual for guidelines on how the various imaging studies should be performed.
w. If not performed within the last 8 weeks.
x. 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]).
y. Confirmatory scans: Minimum of 4 weeks (e.g., 28 days) after the first tumor evaluation showing a CR or PR by RECIST 1.1 or RANO, as appropriate to tumor type, if permitted by regulatory authorities. The next scan should continue according to the schedule above.
z. Study sites will conduct a telemedicine visit when no in-clinic visit occurs to confirm whether the patient is experiencing any new, or changes to existing, AEs/SAEs and concomitant medications, and to confirm study drug compliance and missed doses.
aa. Up to 1-hour pre-dose, and post-dose 1, 2, and 4 hours (±15 minutes) and 8 hours (±30 minutes). For intra-patient dose escalation, PK samples should be collected pre-dose (up to 1 hour prior to dosing) and post-dose at 1, 2, and 4 hours (±15 minutes) and 8 hours (±30 minutes) on Day 8 (±3 days) of the patient's new dose.
bb. EORTC QLQ-C30 (patients 18 years and older) and PedsQL (patients age 12-17 years). 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.
cc. Only for patients with a diagnosis of MTC and diarrhea at baseline. For Cycle 7 and beyond, the patient should personally maintain bowel diary and discuss the diary with the site during telemedicine visits. The bowel diaries should be returned at the next in-clinic visit or provided to study site electronically.
dd. AEs and SAEs should be recorded from the time that written informed consent has been obtained through the SFU Visit.
ee. Concomitant, ongoing medication(s) plus those administered within 14 days prior to the planned start of treatment.
ff. Patients will be followed for survival status, date of progression, and subsequent anticancer therapy(ies) by telephone or other method.
gg. This is required for adolescents who have not reached adult height (see Section 7.8.6).

Table 7-2 Continued Access Schedule of Assessments

Visit	Study Treatment	SFU[a]	LTFU	Instructions
Procedure[b]				
Adverse events	X	X		Collect throughout the study.
Selpercatinib administration	X			
Survival	X		X	MTC patients ONLY. Patients who discontinue treatment and 30-day follow up will be followed for survival until End of Study
Progression Date and Type	X	X	X	Only for MTC patients who have not had radiographic progression. Type = radiographic or clinical

a. Safety Follow-Up (SFU): 28 days (+7 days) after final dose of study drug.
b. Clinic visits during continued access should continue at a minimum of every 84 ± 7 days for IP dispensing. Additional visits may be performed as clinically indicated.

7.1 Screening Period

The following 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 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. Screening tests that are completed in the 48 hours prior to start of study drug administration and that duplicate C1D1 tests according to the Schedule of Assessments (Table 7-1) will be accepted as fulfilling the C1D1 assessments; repeat testing on C1D1 is not necessary for this scenario, and results should be recorded in the Screening set of eCRFs.

- 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 anonymized/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 ~25 × 5 um unstained slides. If archived tumor tissue is not available or is of insufficient quantity or quality, a fresh tumor biopsy should be obtained prior to selpercatinib. If in the opinion of the Investigator, a fresh biopsy cannot be safely performed, the patient may still be eligible with prior Sponsor approval.
- Physical examination, including relevant review of systems, body weight and height, and ECOG performance status or Lansky Performance Score (refer to Appendix F).
- Vital signs, including systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature.
- Resting 12-lead ECG.
- 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).
- Hematology, including hemoglobin, hematocrit, RBC count, WBC count with differential (neutrophils [count and percent] and lymphocytes, monocytes, eosinophils, basophils [percent]), and platelet count.
- Serum chemistries (non-fasting), blood urea nitrogen (BUN; urea is acceptable for countries where BUN is not tested), total cholesterol, creatinine, glucose, lactate dehydrogenase (LDH), sodium, potassium, calcium, chloride, bicarbonate, magnesium, phosphorus, albumin, and total protein.
- LFTs, including ALT, AST, alkaline phosphatase, and total and direct bilirubin.
- Thyroid panel, including thyroid-stimulating hormone (TSH), free triiodothyronine (T_3), and free thyroxine (T_4).
- Urinalysis, including color, appearance, specific gravity, pH, glucose, bilirubin, ketones, occult blood, protein, leukocytes, nitrites, and urobilinogen.

- 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.
- Serum cortisol, Serum ACTH, 24-hour urine for free cortisol: optional for patients with Cushing's disease related to their cancer.
- Participants under age 18 who have not yet obtained full adult height should undergo radiograph of one knee at baseline for growth plate assessment.
- Whole blood for genomic DNA: obtained any time within 28 days prior to treatment on C1D1.
- 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.
    - 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 (chest CT does not require IV contrast) 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.

  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. See 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 or RANO as appropriate to tumor type (refer to Section 7.8.1).
  - 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 and PK, which must be performed relative to the dose of selpercatinib on that day as indicated below.

Laboratory values on C1D1 pre-dose must meet the inclusion/exclusion criteria for treatment to proceed.

Day 1

- Symptom-directed physical examination, weight, and ECOG or Lansky score.
- Vital signs.
- 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).
- Hematology (as described in Section 7.1).
- Serum chemistries (as described in Section 7.1).
- Liver function tests (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.
- Serum cortisol, serum 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.
- Whole blood for cfDNA analysis: obtained prior to treatment on C1D1.
- 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.

- For patients 18 years or older: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30).
- For patients age 13 to 17 years: Pediatric Quality of Life Inventory-Core Module (PedsQL) for teens.
- For patients age 12 years: PedsQL for children.

Day 8

- Symptom-directed physical examination, weight, and ECOG or Lansky score.
- Vital signs.
- Resting 12-lead ECG: 2 hours post-dose (±10 minutes) and prior to PK blood draw at this time point. Further ECGs may be required based upon results of the 2 hours post-dose ECG (refer to Table 7-1, footnote "j" for specific instruction based upon QTcF value observed).
- Blood sample for PK (2 mL whole blood): pre-dose (within 1 hour prior to dosing), and post-dose at 1, 2 and 4 hours (±15 minutes) and 8 hours (±30 minutes).
- Selpercatinib administration.
- 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 or Lansky score.
- Vital signs.
- Hematology (as described in Section 7.1).
- Serum chemistries (as described in Section 7.1).
- LFTs (as described in Section 7.1).
- Thyroid panel, including TSH, free T_3, and free T_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.
- Serum cortisol, serum 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.

- Whole blood for cfDNA analysis.
- Selpercatinib administration.
- 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 22

Telephone contact for safety: The site will contact the patient by telephone to assess for selpercatinib tolerability, continuation of study drug, and whether the patient needs to return to the clinic earlier than planned. If not tolerating the drug well, the patient should be seen at least every 14 days to assess AEs, and the patient should be contacted regularly to assess AE status. The patients should be reminded to complete the bowel diary for the previous week and bring the diary to the C2D1 visit.

7.3 Cycles 2 and Higher

The following procedures will be performed prior to dosing as noted. Routine clinic visits performed within ±3 days of the nominal visit day will not be considered protocol deviations.

- Symptom-directed physical examination, weight, and ECOG or Lansky score: Day 1 of each cycle starting with C2. Beyond Cycle 7, physical examination is only required when the patient returns to the clinic for disease assessment cycles (C7, C9, C11, and C13, then every 12 weeks [Q12W] thereafter).
- Vital signs: Day of 1 each cycle starting with C2. Beyond Cycle 7, vital signs are only required when the patient returns to the clinic for disease assessment cycles (C7, C9, C11, and C13, then Q12W thereafter).
- Resting 12-lead ECG (2 hours post-dose on C2D1, C3D1, C4D1, C5D1 and C6D1 [±10 minutes]) and subsequently in alignment with required disease assessment timepoints (C7, C9, C11, and C13, then Q12W thereafter through Cycle 26). Further ECGs may be required based upon results of the 2 hours post-dose ECG (refer to Table 7-1, footnote "j" for specific instruction based upon QTcF value observed). Additional ECGs may be performed if clinically indicated.
- 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 of each cycle starting with C2. For Cycle 7 and beyond, patients may have serum or urine pregnancy test completed at local healthcare facilities during non-disease assessment cycles.
- Hematology (as described in Section 7.1): Day 1 of each cycle starting with C2. For Cycle 7 and beyond, patients may have hematology completed at local healthcare facilities during non-disease assessment cycles.

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 Section 7.1): Day 1 of each cycle starting with C2. For Cycle 7 and beyond, patients may have serum chemistries completed at local healthcare facilities during non-disease assessment cycles.

  Note: Patients found to have treatment-emergent laboratory toxicity of Grades 3 or 4 will be monitored at least weekly until resolution.
- LFTs (as described in Section 7.1): C2D1, C2D15, C3D1, C3D15, and D1 of each cycle starting with C4. For Cycle 7 and beyond, patients may have LFTs completed at local healthcare facilities during non-disease assessment cycles.

  Note: Patients found to have treatment-emergent laboratory toxicity of Grades 3 or 4 will be monitored at least weekly until resolution.
- Thyroid panel: C3D1 and then ±7 days of each radiologic disease assessment.
- Urinalysis: Beyond C1D15, urinalysis is only required when clinically indicated.
- Calcitonin, CEA: for patients with MTC only; should be measured C2D1 and then ±7 days of each radiologic disease assessment. 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); should be measured C2D1 and then ±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.
- Serum cortisol, serum ACTH, 24-hour urine for free cortisol: for patients with Cushing's disease related to their cancer; should be measured C2D1 and then ±7 days of each radiologic disease assessment. If done, urine collection should begin pre-dose.
- Participants under age 18 who have not yet obtained full adult height should undergo radiograph of one knee every 6 months for growth plate assessment. Image the same knee that was imaged at baseline.
- Whole blood for cfDNA analysis: C2D1 only
- 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 see 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 or RANO is encouraged. If this scan is performed, the next scan should continue according to the schedule above.

- Outpatient diaries for recording daily selpercatinib dosing, PPIs, H2 blockers, and antacids (refer also to Restricted Concomitant Medications, Section 6.3.3).
- AEs.
- Concomitant medications.
- Patient-reported outcomes:
  - For MTC patients with diarrhea present at baseline: bowel diary, Day 1 of each cycle starting with C2.
  - For patients 18 years or older: EORTC QLQ-C30 completed at the same cycle visits as disease assessments until EOT.
  - For patients age 13 to 17 years: PedsQL for teens completed at the same cycle visits as disease assessments until EOT.
  - For patients age 12 years: PedsQL for children completed at the same cycle visits as disease assessments until EOT.

7.4 Intra-Patient Dose Escalation

As discussed in Section 3.4, intra-patient dose escalation may be permitted by the Sponsor following completion of the 28-day DLT period in Cycle 1. Please note that this guidance applies to Phase 1 intra-patient dose escalation, and does not apply to patients who dose reduce and are re-escalated to the starting dose.

The following procedures will be performed (refer to Table 7-1):

- Day 1 of new dose (±3 days):
  - Symptom-directed physical examination, weight, and ECOG or Lansky score.
  - Vital signs.
  - Resting 12-lead ECGs: pre-dose, up to 4 hours pre-dose),2 hours postdose- (±10 minutes). Further ECGs may be required based upon results of the 2 hours post-dose ECG (refer to Table 7-1, footnote "j" for specific instruction based upon QTcF value observed).
  - Hematology (as described in Section 7.1).
  - Serum chemistries (as described in Section 7.1).
- Day 8 of new dose (±3 days):
  - Symptom-directed physical examination, weight, and ECOG or Lansky score.

- Vital signs.
- Resting 12-lead ECG: 2 hours post-dose (±10 minutes) prior to blood draw for PK sample if performed at this time point. Further ECGs may be required based upon results of the 2 hours post-dose ECG (refer to Table 7-1, footnote "j" for specific instruction based upon QTcF value observed).
- LFTs (as described in Section 7.1).
- Blood sample for PK (2 mL whole blood): pre-dose (within 1 hour prior to dosing) and post-dose at 1, 2 and 4 hours (±15 minutes) and 8 hours (±30 minutes).

If Day 1 of the new dose falls on the same day (±3 days) of a previous hematology and serum chemistry assessment, and LFTs, it is not necessary to perform a repeat assessment (exam, vital signs, and ECGs must still be performed as indicated). Patients found to have treatment-emergent laboratory toxicity of Grades 3 or 4 will be monitored at least weekly until resolution.

Requests for intra-patient dose escalation must be made to the Sponsor prior to treating a patient with a new dose. Treatment with a new dose should start on Day 1 (±3 days) of a cycle unless discussed with the Sponsor.

Exceptions to these assessments will not be considered protocol violations if approved by the Sponsor.

7.5 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:

- 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 or Lansky score.
- Vital signs.
- Resting 12-lead ECG: only if prior ECG reading showed treatment-emergent abnormalities.
- Hematology (as described in Section 7.1).
- Serum chemistries (as described in Section 7.1).
- 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).
- LFTs (as described in Section 7.1).
- 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.

- Serum cortisol, serum ACTH, 24-hour urine for free cortisol: optional for patients with Cushing's disease related to their cancer.
- Whole blood for cfDNA analysis: obtained at the EOT visit even if radiologic disease assessment is not performed.
- 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:

o For MTC patients with diarrhea present at baseline: Bowel diary.

o For patients 18 years or older: EORTC QLQ-C30.

o For patients age 13 to 17 years: PedsQL for teens.

o For patients age 12 years: PedsQL for children.

7.6 Safety Follow-Up Visit

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 or Lansky score.
- Vital signs.
- Resting 12-lead ECG.
- Hematology (as described in Section 7.1).
- Serum chemistries (as described in Section 7.1).
- 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).
- LFTs (as described in Section 7.1).
- Urinalysis.
- AEs.
- Status of unresolved SAEs (if unresolved SAEs exist at the time of this visit, subsequent assessment for resolution may be conducted by phone if the patient is not able to return to the clinic).

- Concomitant medication(s).

7.7 Long-Term Follow-Up

After treatment discontinuation, 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. 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.

7.8 Procedures for Special Tests

7.8.1 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) or RANO criteria (Appendix H) as appropriate to tumor type; or a comparable assessment method depending on location of tumor.

7.8.2 Central Collection of Radiographic Studies

Baseline screening radiographic studies and all subsequent radiographic studies and their associated reports will be collected and stored for future independent radiological review.

7.8.3 Pharmacokinetics

Plasma samples will be obtained for patients as outlined in Section 7. 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.

Plasma samples will be obtained on C1D8 and D8 of a patient's new dose (if the patient is intra-patient dose escalated). 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 PKs 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.

7.8.4 Collection of EORTC QLQ-C30, PedsQL for Teens, PedsQL for Children, and Bowel Diary

Paper HRQoL instruments will be administered pre-dose on C1D1.

The EORTC QLQ-C30, PedsQL for teens, or PedsQL for children questionnaires and a bowel diary (for MTC patients only) will be used as appropriate for the patient (refer to Appendix I) and should be implemented for newly enrolled patients. Only patients who have completed questionnaires at baseline should complete subsequent questionnaires at the specified follow-up periods.

For EORTC QLQ-C30, PedsQL for teens, or PedsQL for children, 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.

7.8.5 Correlative Studies

7.8.5.1 Archived Tumor Samples

Archived tumor samples prior to treatment with selpercatinib are required if available for participation in the trial. Tissue blocks are preferred, otherwise ~25 × 5 um unstained slides, with verification of at least 20% tumor content, should be provided. If sufficient quantity or quality of tissue cannot be provided, patients should undergo a fresh tumor biopsy, if it is considered safe to perform, prior to treatment (refer to Section 7.8.5.2). The samples will be used for identification or confirmation of molecular abnormalities in *RET* and other genes.

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.

7.8.5.2 Fresh Tumor Biopsies

Fresh tumor samples will be used to identify putative mutations arising in the *RET* gene (or other genes) that may confer acquired resistance to selpercatinib (or prior MKIs with anti-RET activity) and for other investigations into potential causes of acquired resistance. 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 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 7.8.5.1) and for whom, in the opinion of the Investigator, a fresh tumor biopsy can be safely performed. 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.

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).

At progression after treatment with selpercatinib

Optional: A fresh biopsy of a lesion should be obtained if oligometastatic disease constituting progression on selpercatinib is identified, the patient provides informed consent, and it can be safely performed. The purpose of the fresh tumor biopsy is to evaluate tumor changes that may have resulted from treatment.

Optional: A fresh biopsy of a lesion should be obtained if overt progression on selpercatinib is reported, the patient provides informed consent, and it can be safely performed. The purpose of the fresh tumor biopsy is to evaluate tumor changes that may have resulted from treatment.

The biopsy (Table 7-3) must be captured on the appropriate eCRF and requisition page(s). Refer to the Laboratory Manual for detailed sample collection, storage, and shipment information.

Table 7-3 Tissue/Whole Blood Sampling upon Progression

For patients who progress during therapy, biopsy upon progression should be done if clinically safe to perform and if the patient consents. The clinician should consider if study therapy will continue beyond progression or be discontinued due to progression.	
Scenario	**Sampling**
At time of progression **where study therapy will be discontinued**	Tumor tissue sample from patients who experienced PD and consent to biopsy, if it does not jeopardize the patient's health Whole blood for cfDNA analysis
At any progression, including if the patient will continue study therapy as treatment beyond progression	Whole blood for cfDNA analysis Optional tumor biopsy

Abbreviations: cfDNA = circulating free tumor DNA; PD = progressive disease.

7.8.5.3 Blood Biomarkers

Whole blood will be collected for evaluating cfDNA pre-dose C1D1, C1D15 and C2D1; and at the time of progression and/or EOT. If oligometastatic disease constituting progression is

identified but the patient is otherwise stable and will continue selpercatinib beyond progression, patients should continue to have blood collected for cfDNA analysis (refer to Laboratory Manual) at the time of each progression, to evaluate tumor changes that may have resulted from treatment.

If overt progression is reported and study drug therapy will be discontinued (i.e., EOT), patients should have blood collected for cfDNA analysis (refer to Table 7-3 to evaluate tumor changes that may have resulted from treatment.

The primary purposes of collection of blood for cfDNA analysis are to identify early indicators of selpercatinib treatment efficacy (e.g., by measuring a decrease in cfDNA) and to identify potential mechanisms of resistance through the identification of new genetic alterations that arise in the *RET* or other genes at progression after treatment with selpercatinib.

In addition, a whole blood sample collected at Screening may be used for DNA sequencing to determine the somatic or germline origin of mutations identified from analysis of archival or fresh tumor samples. Biomarker analyses will not produce interpretable results on germline DNA and therefore no incidental findings will be reported.

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.

7.8.5.4 *Biomarker Samples*

Archived tumor, fresh biopsy, and blood samples may be assessed by various methods including gene panel sequencing and DNA candidate gene studies. Regardless of the technology utilized, data generated will be used only for the specific genomic research scope described in the study objectives or to develop research methods and validate new diagnostic tools or assays.

7.8.6 Growth Plate Monitoring

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

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

7.8.7 Thyroid Function

Hypothyroidism was reported in patients receiving selpercatinib in clinical trials. Monitor patients for hypothyroidism and treat as medically appropriate. Baseline laboratory measurement of thyroid function is recommended in all patients. Patients with pre-existing hypothyroidism should be treated as per standard medical practice prior to the start of selpercatinib treatment. All patients should be observed closely for signs and symptoms of thyroid dysfunction during selpercatinib treatment. Thyroid function should be monitored periodically throughout treatment with selpercatinib. Patients who develop thyroid dysfunction should be treated as per standard medical practice, however patients could have an insufficient response to substitution with levothyroxine (T4) as selpercatinib may inhibit the conversion of levothyroxine to liothyronine (T3) and supplementation with liothyronine may be needed.

7.9 Continued Access

Participants who are still on study intervention at the time of study completion may continue to receive study intervention in the continued access period if they are experiencing clinical benefit and no undue risks. The continued access period will apply to this study only if at least 1 participant is still on study treatment when study completion occurs. The Sponsor will notify investigators when the continued access period for each participant begins based on cohort assignment or other relevant parameters.

Participants are not required to sign a new ICF before treatment is provided during the continued access period; as of Protocol Amendment 11, the ICF includes information on continued access.

The participant's continued access to study treatment will end when a criterion for discontinuation is met (Section 6.4). Continued access follow-up will begin when the participant and the investigator agree to discontinue study treatment and lasts approximately 30 days (±7).

Follow-up procedures will be performed as shown in the Continued Access SoA (see Table 7-2).

Participants who are in short-term follow-up when the continued access period begins will continue in short-term follow-up until the 30-day short-term follow-up visit is completed. Participants who are in long-term follow-up when the continued access period begins will be discontinued from study.

During Continued Access, long-term follow-up does not apply. Survival and progression information will be collected only for MTC patients (see Table 7-2).

In all cases, no follow-up procedures will be performed for a participant who withdraws informed consent unless he or she has explicitly provided permission and consent.

8. PLANNED ANALYSES

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

8.1 Study Endpoints

Primary Endpoint (Phase 1)

- MTD/RP2D

Secondary Endpoints (Phase 1)

- Frequency, severity, and relatedness of TEAEs and 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 area under the concentration versus time curve from time 0 to 24 hours (AUC_{0-24}), C_{max}, time to maximum plasma concentration (T_{max}), and degree of accumulation
- ORR based on RECIST 1.1 or RANO, as appropriate to tumor type

Primary Endpoint (Phase 2)

- ORR based on RECIST 1.1 or RANO, as appropriate to tumor type, assessed by IRC

Secondary Endpoints (Phase 2)

- Parameters of anti-tumor activity/clinical benefit, including: ORR (by Investigator), best change in tumor size from baseline (by IRC and 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_{0-24}, C_{max}, and T_{max}

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
- Identity of *RET* gene fusions, mutations, and concurrently activated oncogenic pathways in tumor biopsies and cfDNA
- Changes from baseline in disease-related symptoms and HRQoL, as measured by EORTC QLQ-C30 (adults), PedsQL for teens (ages 13-17 years), PedsQL for children (age 12 years), and patient bowel diaries (MTC patients only)

8.2 Analysis Populations

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

8.2.1 Safety Analysis Set

The Safety Analysis Set will be used for the analysis of safety data and will consist of all enrolled patients who receive at least one dose of selpercatinib. A baseline measurement of 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.

The analysis populations for other trial objectives (e.g., PK, tumor markers) will be defined in the Statistical Analysis Plan.

8.3 Determination of Sample Size

Phase 1

Three to 6 patients will be enrolled in each dose cohort based on a 3+3 design. Each patient will participate in only a single dose cohort for the purpose of DLT evaluation (though, as discussed in Section 3.4, after completion of the DLT evaluation period, intra-patient dose escalation may be permitted, provided that the patient is tolerating their current dose, and the dose level to which the patient will be escalated has already been evaluated, has a DLT rate of < 33%, and has been declared safe by the SRC).

A starting sample size of at least 3 patients per dose cohort, expanding to 6 patients in the event of a marginal DLT rate (30%) was deemed to be a safe and conventional approach in the dose escalation of a novel oncologic agent. Assuming a true DLT rate of 5% or less, there would be a 3% chance that dose escalation would be halted in a given cohort (i.e., observing 2 or more patients with DLT). If a true DLT rate of 50% is assumed, then there would be an 89% chance that dose escalation would be halted in a given cohort.

During Phase 1, selected dose cohorts previously declared safe by the SRC may be expanded to a total of approximately 15 patients to further investigate the tolerability, PK, and biological activity of selpercatinib.

The total number of patients to be enrolled in Phase 1 is dependent upon the observed safety profile, which will determine the number of patients per dose cohort, as well as the number of dose escalations required to achieve the MTD/RP2D for further study. If approximately 15 patients are enrolled in each planned dose cohort (Cohorts 1–8), a total of approximately 120 patients will be enrolled in Phase 1.

Phase 2

For Cohort 1 (patients with RET fusion-positive solid tumors who have progressed on or are intolerant to standard first-line therapy for their cancers), a true ORR of ≥ 50% is hypothesized when selpercatinib is administered to patients with such malignancies. A sample size of 55 patients is estimated to provide 85% power to achieve a lower boundary of a two-sided 95% exact binomial confidence interval (CI) about the estimated ORR that exceeds 30%. Ruling out a lower limit of 30% is considered clinically meaningful and consistent with the estimated response rates seen with approved targeted therapies in molecularly-defined patient populations who have failed prior therapies (e.g., osimertinib [Tagrisso®], crizotinib [Xalkori®], alectinib [Alecensa®], and others).

For Cohort 2 (patients with RET fusion-positive solid tumors without prior standard first-line therapy), a true ORR of ≥ 55% is hypothesized when selpercatinib is administered to such patients. A sample size of 59 patients is estimated to provide 85% power to achieve a lower boundary of a two-sided 95% exact binomial CI about the estimated ORR that exceeds 35%. For Cohort 3 (patients with RET-mutant MTC who have progressed on or are intolerant to vandetanib and/or cabozantinib), a true ORR of ≥ 35% is hypothesized when selpercatinib is administered to such patients. A sample size of 83 patients is estimated to provide 85% power to achieve a lower boundary of a two-sided 95% exact binomial CI about the estimated ORR that exceeds 20%. Ruling out a lower limit of 20% is considered clinically meaningful in patients who have failed prior MKI therapy (e.g., cabozantinib) and currently have limited treatment options for their advancing disease.

For Cohort 4 (patients with RET-mutant MTC who are MKI-naïve), a true ORR of ≥ 50% is hypothesized when selpercatinib is administered to such patients. A sample size of 55 patients is estimated to provide 85% power to achieve a lower boundary of a two-sided 95% exact binomial CI about the estimated ORR that exceeds 30%.

Notwithstanding the statistical considerations above, if approved by the SRC, enrollment beyond the above sample sizes in each of Cohorts 1-5, will be allowed, in order to accommodate enrollment demand and allow for the characterization of AEs that may occur with low frequency. With a sample size of 150 patients, the probability of observing one or more instances of a specific AE within a cohort with a true incidence rate of 1% and 2% is 77.9% and 95.2%, respectively. The sample size for Cohort 1 was increased to ~250 to accommodate enrollment demand. Additional enrollment will also allow for the characterization of AEs that may occur with low frequency which would enhance knowledge of the safety profile of selpercatinib. Further, this cohort allows for the enrollment of patients with RET fusion-positive solid tumors other than NSCLC. While the enrollment demand for patients with RET fusion-positive NSCLC has been adequate for statistical analysis, additional solid tumor types remain underrepresented and enrollment expansion allows for data capture in this population.

Up to ~50 patients will be enrolled into Cohort 6 based on clinical consideration. Exploring efficacy in patients with a history of prior exposure to RET specific inhibitors may enhance

understanding of the risk:benefit of additional RET specific therapy in these patients and aid in the consideration of resistance mechanisms in response to this type of therapy.

8.4 Futility Monitoring

A futility analysis of the response rate (including confirmed or unconfirmed PR or CR) will be performed after every 25 subjects are enrolled for each cohort of Cohorts 1-5. The purpose of the futility assessment is to safeguard future patients from exposure to unequivocally inferior treatment. A response rate of less than 10% (null hypothesis) is deemed as futile. The stopping boundaries are specified as following with Lan-DeMets (O'Brien-Fleming) spending function. If at least 1, 2, 7, 13 and 18 responders are observed from the first 25, 50, 75, 100 and 125 subjects enrolled, then enrollment will proceed without interruption. Otherwise, enrollment will be halted pending the results of each futility assessment. If the true ORR is at least 20%, the probability of stopping at each futility analysis is less than 3%. If the true ORR is significantly higher than that hypothesized (i.e., 50%) the probability is close to zero.

The information fractions and futility boundaries based on a sample size of 150 patients are outlined in Table 8-1.

Table 8-1 Futility Assessment: Information Fractions and Futility Boundaries

Look #	Information Fraction	Sample Size	Futility Boundary		Incremental Boundary Crossing Probabilities	
			Response Rate	Responder (n)	Under H0: $\pi = 0.1$	Under H1: $\pi = 0.2$
1	0.167	25	0	1	0	0
2	0.333	50	0.035	2	0.064	0.002
3	0.500	75	0.093	7	0.357	0.009
4	0.667	100	0.121	13	0.340	0.017
5	0.833	125	0.137	18	0.160	0.021

Note: The information fractions and futility boundaries are based on a sample size of 150 patients.

The information boundaries based on sample sizes of 250, 200 and 50 patients are outlined in Table 8-2, Table 8-3, and Table 8-4, respectively. For each look, if the number of responders specified under the futility boundary is observed, enrollment will proceed without interruption.

Table 8-2 Futility Assessment for a sample size of 250

Look #	Information Fraction	Sample Size	Futility Boundary		Incremental Boundary Crossing Probabilities	
			Response Rate	Responder (n)	Under H0: $\pi = 0.1$	Under H1: $\pi = 0.2$
1	0.1	25	0.000	1	0.000	0.000
2	0.2	50	0.000	1	0.000	0.000
3	0.3	75	0.000	1	0.000	0.000
4	0.4	100	0.040	5	0.021	0.000

Look #	Information Fraction	Sample Size	Futility Boundary		Incremental Boundary Crossing Probabilities	
			Response Rate	Responder (n)	Under H0: $\pi = 0.1$	Under H1: $\pi = 0.2$
5	0.5	125	0.072	10	0.131	0.000
6	0.6	150	0.094	15	0.256	0.000
7	0.7	175	0.110	20	0.259	0.001
8	0.8	200	0.121	25	0.176	0.002
9	0.9	225	0.130	30	0.092	0.002

Table 8-3 Futility Assessment for a sample size of 200

Look #	Information Fraction	Sample Size	Futility Boundary		Incremental Boundary Crossing Probabilities	
			Response Rate	Responder (n)	Under H0: $\pi = 0.1$	Under H1: $\pi = 0.2$
1	0.125	25	0.000	1	0.000	0.000
2	0.25	50	0.000	1	0.000	0.000
3	0.375	75	0.039	3	0.039	0.000
4	0.5	100	0.081	9	0.222	0.001
5	0.625	125	0.105	14	0.320	0.003
6	0.75	150	0.122	19	0.232	0.005
7	0.875	175	0.133	24	0.116	0.007

Table 8-4 Futility Assessment for a sample size of 50

Look #	Information Fraction	Sample Size	Futility Boundary		Incremental Boundary Crossing Probabilities	
			Response Rate	Responder (n)	Under H0: $\pi = 0.1$	Under H1: $\pi = 0.2$
1	0.5	25	0.156	4	0.827	0.293

8.5 Statistical Methods

8.5.1 Demographics and Baseline Characteristics

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

8.5.2 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 8.2.1. The results of these analyses will be presented by tumor indication.

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, including but not limited to the coding plan and data management plan.

TEAEs will be summarized based on the number and percentage of patients experiencing the event by MedDRA System Organ Class and preferred term. 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 9.3. 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.
- SAEs with action of study drug delayed/interrupted or treatment reduced.

The observed DLT rate in each dose cohort will be calculated by the crude proportion of patients who experience DLT. Multiple concurrent AEs leading to DLT will be considered a single DLT. The estimate of the DLT rate will be accompanied by a 2-sided 95% exact binomial CI.

All deaths, including on-study deaths, 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. For patients undergoing LTFU, the duration of survival following the initiation of study drug will be summarized in a descriptive manner using the Kaplan-Meier method. 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, as follows:

- Baseline value
- Minimum post-baseline value

- Maximum post-baseline value
- Average post-baseline value
- Last post-baseline value.

Laboratory values will be assigned toxicity grades when available using the NCI CTCAE, version 4.03. Directional shifts in laboratory toxicity grades (comparing baseline grade with worst post-baseline grade) will be analyzed using standard shift tables, presenting number and proportion of patients and their maximum grade shift. For analytes without a toxicity grading scale, the shift table will present directional shifts from baseline to above or below the laboratory standard normal range using the maximum increase and/or decrease observed throughout the course of treatment/observation.

All patients will have pre-treatment baseline vital signs and pre-dose measurements on D1 of each cycle. The results for each vital sign will be summarized in a descriptive manner by calculating the mean, standard deviation, median, and range by time point in the same manner described for laboratory values. For these analyses, the minimum, maximum, average, and last post-baseline value will be determined relative to the baseline vital sign measurements only. In addition, serial vital signs measurements will be obtained pre- and post-dose on the first day of each patient's selpercatinib treatment in conjunction with serial PK sampling. For each patient, the vital signs change from the pre-dose value will be summarized in a descriptive manner. The Wilcoxon signed rank test may be used to assist in the identification of any systematic changes.

Prior and concomitant medications will be coded using the World Health Organization Drug (WHO Drug) Dictionary; the WHO Drug version shall be specified in study documents, including but not limited to the study coding plan and data management plan.

8.5.3 Efficacy Analyses

The efficacy analyses will be conducted on the Safety Analysis Set of patients with at least 6 months of treatment from the first dose of selpercatinib. These analyses will be summarized per tumor indication, including patients from both the Phase 1 and Phase 2 portions. A Statistical Analysis Plan (SAP) will provide specific details on the efficacy analysis set.

ORR will be assessed using RECIST 1.1 (Table 11-9) or RANO (Table 11-11, for patients with primary CNS tumors), as appropriate to tumor type. The estimate of the ORR will be calculated based on the maximum likelihood estimator (i.e., crude proportion of patients with best overall response of CR or PR that are confirmed based on RECIST 1.1 or RANO). The estimate of the ORR will be accompanied by 2-sided CIs with various coverage probabilities (e.g., 80%, 95%). The analysis of ORR will be conducted both by the responses determined by each Investigator and responses as determined by IRC.

Waterfall plots will be used to depict graphically the maximum decrease from baseline in the sum of longest 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 according to the censoring methods described later in this section. Whenever appropriate, the same censoring methods will be used for DOR.

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.

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).

For patients who meet one or more of the following conditions, DOR and PFS will be right-censored as appropriate:

- Patients with no baseline or post-baseline disease assessments unless death occurred prior to the first planned post-baseline assessment (in which case the death will be considered a PFS event)
- Patients who initiate subsequent anticancer therapy in the absence of documented PD
- Patients who die or have PD after missing 2 or more consecutively scheduled disease assessment visits
- Patients who are last known to be alive and without documented PD on or before the data cut-off date

For such patients, the progression or censoring date will be determined based on described conventions (U.S.-Food-and-Drug-Administration 2007).

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

8.5.4 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 if feasible: 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 (Vz/F), and

$t_{1/2}$. If appropriate, those PK parameters may also be calculated from plasma concentrations on C1D1, C3D1, and C5D1.

Summary statistics will be generated by dose cohort and across cohorts as appropriate.

9. ADVERSE EVENTS

An AE is any unfavorable medical occurrence in a patient administered an investigational product, which does not necessarily have a causal relationship with the treatment. Events meeting the AE definition include medication error, misuse, or abuse of IMP, including signs, symptoms, or clinical sequelae.

An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of the investigational product, whether or not considered related to the investigational product. All AEs that occur prior to the first dose are considered medical history unless the AE develops or worsens due to study related procedures. All SAEs, regardless of causality, that occurred from time of informed consent to SFU are to be recorded on the appropriate eCRF. Documentation must be supported by an entry in the patient's source medical records. Laboratory test abnormalities considered by the Investigator to be clinically relevant should be reported in the eCRF as an AE. Each AE is to be evaluated for duration, severity, and causal relationship with the investigational product or other factors. Serious AEs, including death, caused by disease progression should not be reported unless the investigator deems them to be possibly related to study treatment.

9.1 Safety Review Committee

An SRC will be established to oversee the safety aspects of the Phase 1 portion of the study, and to render dose escalation decisions. Specifically, the SRC will perform ongoing review and adjudication of SAEs and other safety trends throughout the conduct of the study. The SRC membership will consist of the Sponsor's Medical Monitor, a Clinical Operations representative, and the Principal Investigator (or clinically qualified designee) from each active clinical site contributing patients to that cohort. The SRC will be convened for each cohort dose escalation decision or as needed. The SRC will only be required to convene prior to a cohort dose escalation if there is a DLT reported in a cohort. Decisions will be documented in written minutes.

The SRC established to oversee the safety aspects of the Phase 2 portion of the study will consist, at a minimum, of the Sponsor's Medical Monitor, a Clinical Operations representative, and the Global Principal Investigator. The Phase 2 safety committee will convene at a minimum of every 6 months for the first 5 years of the study, then annually (or more frequently depending on enrollment or observed safety profile) and perform ongoing review of SAEs and other safety-related data throughout the conduct of the study.

9.2 Grading and Intensity of Adverse Events

The Investigator will grade the severity of each AE using, when applicable, the NCI CTCAE, version 4.03. In the event of an AE for which no grading scale exists, the Investigator will classify the AE as mild, moderate, severe, life-threatening, or fatal, as defined below.

- Mild (Grade 1) – An event that is usually transient in nature and generally not interfering with normal activities.
- Moderate (Grade 2) – An event that is sufficiently discomforting to interfere with normal activities.
- Severe (Grade 3) – An event that is incapacitating with inability to work or do usual activity or inability to work or perform normal daily activity.
- Life-threatening (Grade 4) – An event that puts the patient at immediate or potential risk of death.
- Fatal (Grade 5).

9.3 Relationship to Underlying Disease, Other Medical Condition or Concomitant Medications

The Investigator will categorize each AE as to its potential relationship to underlying disease, other medical conditions or concomitant medications using the categories of Yes (causally related) and No (unrelated) as defined below. The assessment of the relationship of an AE to the underlying disease, other medical conditions, or concomitant medications is a clinical decision based on all available information at the time. In the absence of prior human data for this first-in-human study of selpercatinib, if the AE cannot be attributed to the patient's underlying disease, other medical conditions, or concomitant medication, and the temporal relationship of the occurrence of the AE with administration of the study drug suggests, then the AE will be assumed to be due to selpercatinib.

No:
The time course between the occurrence or worsening of the AE and underlying disease, other medical conditions, or concomitant medications rules out a causal relationship and another cause is suspected.

Yes:
The time course between the occurrence or worsening of the AE and the underlying disease, other medical conditions, or concomitant medications is consistent with a causal relationship.

The following factors should also be considered:

- Temporal sequence from treatment with the study drug.
- Preclinical and prior clinical data regarding whether a particular AE could be an effect of the study drug (or class of drug).
- Pharmacology and PK of the investigational product.

An unexpected AE is an experience not previously reported or an AE that occurs with specificity, severity, or frequency that is not consistent with the current selpercatinib IB.

9.4 Serious Adverse Event Reporting

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

- Results in death.
- Is life-threatening.
- Requires hospitalization or prolongation of existing hospitalization.
- Results in disability/incapacity.
- Is a congenital anomaly/birth defect.
- Is an important medical event.

Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious.

Any hospital admission with at least one overnight stay will be considered an inpatient hospitalization. An emergency room visit without hospital admission will not be recorded as an SAE under this criterion, nor will hospitalization for a procedure scheduled or planned before signing of the informed consent. However, unexpected complications and/or prolongation of hospitalization that occur during elective surgery should be recorded as AEs and assessed for seriousness. Admission to the hospital for social or situational reasons (i.e., no place to stay, live too far away to come for hospital visits) will not be considered inpatient hospitalizations.

In the event of an accidental or intentional overdose by a patient, the site staff must immediately inform Medpace Clinical Safety. The eCRF must be updated to reflect this information. In the event that the overdose is associated with an SAE, the two events should be linked. In the event of an AE associated with an overdose, an SAE report form must be completed detailing the AE and the overdose details.

Disease progression (PD) is an efficacy finding and will not be reported as an AE or an SAE.

9.4.1 Serious Adverse Event Reporting – Procedures for Investigators: Initial Report

All SAEs occurring from the time informed consent is signed through 28 days after the last dose must be reported to Medpace Clinical Safety within 24 hours of the knowledge of the occurrence (this refers to any AE that meets any of the aforementioned serious criteria). All SAEs that the Investigator considers related to study drug occurring after the 28-day follow-up period must be reported to the Sponsor.

To report the SAE, complete the SAE form electronically in the EDC system for the study. When the form is completed, Medpace Safety personnel will be notified electronically and will retrieve the form. If the event meets serious criteria and it is not possible to access the internet, send an email to Medpace Safety at medpace-safetynotification@medpace.com or call the Medpace SAE hotline (phone number listed below), and fax the completed paper SAE form to Medpace (fax number listed below) within 24 hours of awareness. When the EDC system becomes available, the SAE information must be entered within 24 hours of the system becoming available.

Safety Contact Information:

Medpace Clinical Safety

Medpace SAE hotline – **USA/Asia-Pacific**:

Telephone: +1-800-730-5779, dial "3" or +1-513-579-9911, dial "3"

Fax: +1-866-336-5320 or +1-513-579-0444

e-mail: medpace-safetynotification@medpace.com

Medpace SAE hotline – **Europe**:

Telephone: +49 89 89 55 718 44

Fax: +49 89 89 55 718 104

e-mail: medpace-safetynotification@medpace.com

The Investigator will be requested to supply detailed information regarding the event. SAEs must also be reported to the IRB/IEC and a copy of that report must be retained at the investigative site and filed in the Investigator Site File in accordance with the requirements of that institution.

Although not considered an AE per se, the Sponsor must be notified of any patient or patient's partner who becomes pregnant during a clinical study.

SAE Regulatory Reporting:

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will evaluate the reported SAEs, including confirmation of relatedness and assessment of expectedness. The sponsor has processes for safety reports for identification, recording, and expedited reporting of SUSARs according to local regulatory requirements. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.

9.5 Serious Adverse Event Follow-Up

For all SAEs occurring during the study, the Investigator must submit follow-up reports to the Sponsor regarding the status of the SAE and the patient's subsequent course until the SAE has

resolved, or until the condition stabilizes or is deemed chronic (in the case of persistent impairment), or the patient dies.

Within 24 hours of receipt of follow-up information, the Investigator must update the SAE form electronically in the EDC system for the study and submit any supporting documentation (e.g., patient discharge summary or autopsy reports) to Medpace Clinical Safety via fax or email. If it is not possible to access the EDC system, refer to the procedures outlined above for initial reporting of SAEs.

9.6 Pregnancy Reporting

If the patient or partner of a patient participating in the study becomes pregnant during the study or within 28 days of discontinuing study drug, the Investigator should report the pregnancy to Medpace Clinical Safety within 24 hours of being notified. Medpace Clinical Safety will then forward the Exposure In Utero form to the Investigator for completion.

A patient becoming pregnant while on study drug will immediately be withdrawn from the study and early termination study procedures will be performed.

The patient or partner should be followed by the Investigator until completion of the pregnancy. If the pregnancy ends for any reason before the anticipated date, the Investigator should notify Medpace Clinical Safety. At the completion of the pregnancy, the Investigator will document the outcome of the pregnancy. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e., postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for reporting an SAE.

10. STUDY ADMINISTRATION

10.1 Regulatory and Ethical Considerations

The investigator will be responsible for reporting to the sponsor or designee significant issues related to participant safety, participant rights, or data integrity.

10.1.1 Regulatory Authority Approval

This study will be conducted in accordance with the standard of International Conference on Harmonisation-Good Clinical Practices (ICH-GCP), an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve human patients. All applicable country and local regulations will also be observed. Compliance with these standards provides assurance that the rights, safety, and well-being of study patients are protected, consistent with the principles in the Declaration of Helsinki, and that the clinical study data are credible.

10.1.2 Ethics Approval

It is the responsibility of the Investigator to ensure that the appropriate IRB/IEC has reviewed and approved this protocol prior to initiating the study. The Investigator must provide the Sponsor or Sponsor's representative with current and revised IRB/IEC membership rosters that include the members' occupations and qualifications. Sites within the US may provide a copy of the US Department of Health and Human Services Assurance Number.

The IRB/IEC must also review and approve the clinical site's ICF, other written information provided to the patient, and all advertisements that may be used for patient recruitment. The Investigator will provide the study monitor with copies of these documents and of dated IRB/IEC approval(s) prior to the start of the study.

If the protocol or the ICF is amended during the study, the Investigator is responsible for ensuring that the IRB/IEC has reviewed and approved these amended documents. Approval of the amended documents must be obtained from the IRB/IEC before implementation and before new patients are consented to participate in the study using the amended version of the ICF. The Investigator must provide the Sponsor with the dated IRB/IEC approval of the amended documents as soon as available.

10.1.3 Patient Informed Consent

Prior to study entry, the Investigator or designee will explain the nature, purpose, benefits, and risks of participation in the study to each patient, patient's legally acceptable representative, or impartial witness. Written informed consent must be obtained prior to the patient entering the study (before initiation of any study-related screening procedure). Sufficient time will be allowed to discuss any questions raised by the patient. The ICF, which will contain all US federally-required elements, all International Conference on Harmonisation (ICH)-required elements, and

Health Insurance Portability and Accountability Act authorization information in a language that is understandable to the patient, must be signed by all patients. The process of obtaining consent will be in compliance with all applicable local and country regulations and ICH requirements.

If the ICF is amended during the study, the Investigator must follow all applicable regulatory requirements pertaining to IRB/IEC approval of the amended form. The clinical site must use the amended ICF for all new patients and must re-consent any ongoing patients with the amended ICF, if instructed to do so by the IRB/IEC.

The sample ICF prepared by the Sponsor may be found in the Study Manual. The consent and re-consenting process should be properly documented in the source documentation.

10.1.4 Serious Adverse Event Notification to the Institutional Review Board/Independent Ethics Committee

Suspected unexpected serious adverse reactions (SUSARs) will be reported to the IRB/IEC according to their institutional policy by the Investigator or Sponsor (or Sponsor designee) according to country requirements. Copies of each report and documentation of IRB/IEC notification and acknowledgement of receipt will be kept in the Investigator's study file.

10.1.5 Sponsor Safety Reporting to Regulatory Authorities

The Sponsor or its representative is required to report certain study events in an expedited manner to the Food and Drug Administration, the European Medicines Agency's EudraVigilance electronic system according to Directive 2001/20/EC, and to all country Regulatory Authorities where the study is being conducted, according to local applicable regulations.

The following describes the safety reporting timeline requirements for SUSARs and other reportable events:

Immediately and within 7 calendar days:

- Any suspected adverse reaction that is associated with the use of the study drug, unexpected, and fatal or life-threatening. Follow-up information must be reported in the following 8 days.

Immediately and within 15 calendar days:

- Any suspected adverse reaction that is associated with the use of the study drug, unexpected, and serious, but not fatal or life-threatening, and there is evidence to suggest a causal relationship between the study drug and the reaction.
- Any finding from tests in laboratory animals that suggest a significant risk for human patients, including reports of mutagenicity, teratogenicity, or carcinogenicity.
- Any event in connection with the conduct of the study or the development of the study drug that may affect the safety of the study patients. In addition, periodic safety reporting

to regulatory authorities will be performed by the Sponsor or its representative according to national and local regulations.

10.2 Data Management

Source documents will be maintained by sites and used to enter data and complete the eCRFs in the clinical database (EDC or Clinical Data Management System [CDMS]). The Sponsor's monitors will routinely review the source documentation and verify the corresponding data entered on eCRFs in the clinical database. All entered, changed, and final data shall be available with a validated audit trail report or data extract report. The eCRFs shall be considered complete when all expected data has been entered and all discrepancies have been resolved or documented.

The Investigator must sign all eCRFs according to the EDC (CDMS) requirements.

10.2.1 Data Protection

Participants will be assigned a unique identifier by the sponsor to protect the participant's personal data. Any participant information, such as records, datasets or tissue samples that are transferred to the sponsor will contain the identifier only. Participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that the participant's personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent. This is done by the site personnel through the informed consent process.

The participant must be informed through the informed consent by the site personnel that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

The sponsor has processes in place to ensure information security, data integrity, and data protection. These processes address management of data transfer, and prevention and management of unauthorized access, disclosure, dissemination, alteration or loss of information or personal data. These processes include appropriate contingency plan(s) for appropriate and timely response in the event of a data security breach.

The transfer of personal data is subject to appropriate safeguards through contractual agreements and processes. The sponsor's processes are compliant with local privacy laws and relevant legislations including the General Data Protection Regulation (GDPR).

10.3 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 Good Clinical Practices (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.

10.4 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.

Reports

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

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

10.5 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.

10.6 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
lenvatinib
alectinib
ponatinib
regorafenib
sunitinib
sorafenib
motesanib
RXDX-105
sitravatinib (MGCD516)

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
14	V804L, V804M, Y806C, E819K, R833C, R844Q, R866W, M848T
15	L881V, A883F/S/T/V, R886W, S891A, S904C/F
16	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 2015, Oh et al. 2015, Wells, Asa et al. 2015, Heilmann, Subbiah et al. 2016, Romei, Casella et al. 2016, Kato 2017, Subbiah et al. 2017).

For all other non-MTC cancers with *RET* mutation, the Sponsor should have final determination regarding eligibility based upon review of all genomic findings.

Appendix C Examples of Validated Oncogenic Drivers

The following are example 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, NTRK* fusion, or activating mutation in *RAS* genes
MTC	Targetable rearrangement involving *ALK, NTRK* fusion, 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

Appendix D Inhibitors and Inducers of CYP3A4

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

Table 11-4 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: AUC = area under the concentration versus time curve; CYP3A4 = cytochrome P450 3A4.
[a] Increases the AUC of the substrate by ≥5-fold.
[b] Increases the AUC of the substrate by 2- to 5-fold.

Table 11-5 Inducers of CYP3A4

Strong inducers [a]	Moderate inducers [b]
avasimibe	bosentan
carbamazepine	efavirenz
enzalutamide	etravirine
phenytoin	modafinil
rifampin	nafcillin
St John's wort	

Abbreviations: AUC = area under the concentration versus time curve; CYP3A4 = cytochrome P450 3A4.
[a] Decreases the AUC of the substrate by ≥80%.
[b] Decreases the AUC of the substrate by 50–80%.

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

Appendix E Proton Pump Inhibitors (PPIs)

Since selpercatinib is more soluble in an acidic environment than a neutral one, absorption may be impacted by stomach acidity. Therefore, the concomitant use of proton pump inhibitors (PPIs) is restricted. If PPIs cannot be avoided, selpercatinib should be taken with food.

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

Omeprazole (Prilosec®)
Esomeprazole (Nexium®)
Lansoprazole (Prevacid®)
Pantoprazole (Protonix®)
Rabeprazole (Aciphex®)
Dexlansoprazole (Dexilant®)

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 house work, 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

Table 11-8 Lansky Performance Status (< 16 years old)

Score	Lansky Description
100%	Fully active, normal
90%	Minor restrictions in strenuous physical activity
80%	Active, but tired more quickly
70%	Greater restriction of play and less time spent in play activity
60%	Up and around, but active play minimal; keeps busy by being involved in quieter activities
50%	Lying around much of the day, but gets dressed; no active playing, participates in all quiet play and activities
40%	Mainly in bed; participates in quiet activities
30%	Bed bound; needing assistance even for quiet play
20%	Sleeping often; play entirely limited to very passive activities
10%	Doesn't play; doesn't get out of bed
0%	Unresponsive

Source: (Lansky, S. B., List M. A. et al. 1987).

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 magnetic resonance imaging (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 (chest CT does not require IV contrast) 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. See Imaging Manual for details.
- Additional scans can be performed as needed to evaluate potential sites of disease.
- Disease assessments will utilize RECIST 1.1 or RANO, as appropriate to tumor type (refer to Section 7.8.1).
- 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 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 see 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 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 or RANO, 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 11-9. 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 11-10.

Table 11-9 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 11-10 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

Abbreviations: CR = complete response; NE = inevaluable; PD = progressive disease; PR = partial response; SD = stable disease.
Source: (Eisenhauer, Therasse et al. 2009). Available at: http://www.eortc.be/recist/documents/RECISTGuidelines.pdf

Appendix H Response Assessment in Neuro-Oncology (RANO) Criteria for Primary CNS Malignancies

The RANO criteria (Ellingson, Wen et al. 2017) were developed to evaluate efficacy of investigational agents in glioblastoma clinical trials, and have been more broadly utilized for lower grade primary CNS malignancies. These criteria were developed in part to address issues faced when assessing some lesions based on MacDonald criteria, particularly lesions with central necrosis and with a T2 component.

Table 11-11 Response Assessment in Neuro-Oncology (RANO) Criteria

RESPONSE CATEGORY	CRITERIA
Complete Response	Disappearance of all measurable and non-measurable enhancing disease Stable or improved non-enhancing FLAIR/T2 lesions No new lesions Clinically stable or improved with no reliance on corticosteroids (except for physiological replacement)
Partial Response	≥ 50% decrease from baseline of all measurable enhancing lesions No progression of non-measurable disease Stable or improved non-enhancing FLAIR/T2 lesions No new lesions Clinically stable or improved, with stable or reduced corticosteroids compared to baseline
Progressive Disease	≥ 25% increase from baseline in enhancing lesions despite stable or increasing steroid dose Significant increase in non-enhancing FLAIR/T2 lesions not attributable to other non-tumor causes Any new lesions Clinical deterioration not attributable to other non-tumor causes and not due to steroid decrease
Stable Disease	Does not meet other criteria for response or progression Stable non-enhancing FLAIR/T2 lesions Clinically stable with stable or reduced corticosteroids compared to baseline

Abbreviations: FLAIR/T2 = T2-weighted fluid-attenuated inversion recovery; RANO = Response Assessment in Neuro-Oncology.

A measurable lesion is evaluated by contrast-enhancing MRI and:

- Has clearly defined margins
- Is visible on two or more axial slices, preferably < 5 mm thick
- At least 10 mm in size if slice thickness is < 5 mm (or 2 × slice thickness if > 5 mm)
- Does not measure a cystic cavity

Non-measurable lesions are those that do not fit the criteria above, and specifically lesions that are cystic, necrotic, or include a surgical cavity should not be considered measurable.

Measurements are calculated by summing the products of perpendicular diameters of all measurable enhancing lesions.

If there are multiple contrast-enhancing lesions, a minimum of the two largest lesions should be measured. However, emphasis should be placed on selecting lesions that allow reproducible repeated measurements. For patients who have multiple lesions for which only one or two are increasing in size, the enlarging lesions should be considered the target lesions for evaluation of response.

Appendix I European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) and PedsQL-Core Module (PedsQL) 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).

PedsQL™ 4.0 Core Module

The Pediatric Quality of Life inventory is a modular tool to measure health-related QOL in children and adolescents and validated for patients age 2 to 18 years. The instrument uses child self-reporting as a generic core measure integrated into disease specific modules to provide one assessment.

References:

PedsQL website: www.pedsql.org

Varni JW, Burwinkle TM, Katz ER, Meeske K, Dickinson P. The PedsQL in pediatric cancer: reliability and validity of the Pediatric Quality of Life Inventory Generic Core Scales, Multidimensional Fatigue Scale, and Cancer Module. Cancer. 2002;94(7):2090-2106 (Varni, Burwinkle et al. 2002).

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 J Examples of Agents Known to Cause QTc Prolongation

QT interval prolongation was reported in patients receiving selpercatinib in clinical trials. Use with caution in patients with such conditions as congenital long QT syndrome or acquired long QT syndrome, or other clinical conditions that predispose to arrhythmias.

Coadministration of medications known to prolong QTc should be avoided if possible.

Table 11-12 Examples of Agents Known to Cause QTc Prolongation

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.crediblemeds.org for a current list of agents known to cause QTc prolongation as well as agents with a possible or conditional risk.

Appendix K Country-Specific Requirements

Germany

This section describes protocol changes applicable for participants in study sites in Germany.

This table describes the changes and provides a rationale for the changes.

Protocol Section Number and Name	Description of the Change	Brief Rationale
Synopsis, Section 3.6 Phase 2, Section 4.2. Inclusion Criteria for Phase 2, Section 4.3. Exclusion Criteria for Phase 1 and Phase 2	Removed language regarding Cohort 7 and modified schema	Per regulatory feedback
Synopsis, Section 3.6. Phase 2	Phase 2: corrected number of cohorts to "six"	Correction
Section 4.1. Inclusion Criteria for Phase 1	Added inclusion criterion 14 for Germany	
Section 6.4 Removal of Patients from Therapy or Assessment	Added note sites in Germany	
Section 7 Tests and Evaluations, Section 7.3 Cycles 2 and Higher	Updates were made to remove language regarding reduced visit frequency and the use of local healthcare facilities	Per regulatory request
Table 7-1 Schedule of Assessments	Footnote for Cycle 7 and beyond was modified; Note was added for footnote z to exclude Germany; footnote cc was revised to remove telemedicine.	Per regulatory request
Section 8.3. Determination of Sample Size	Added language to justify the increase of sample size	Per regulatory request
Appendix L Provisions for Changes in Study Conduct During Exceptional Circumstances	Appendix L does not apply to Germany	Per regulatory request

The revised text in the following sections show the changes applicable for adult participants at study sites in Germany. Deletions are identified by ~~strikethrough format~~.

Synopsis

- Cohort 6: Patients otherwise eligible for Cohorts 1-5 who discontinued another selective RET inhibitor(s) may be eligible with prior Sponsor approval (up to ~50 patients).
- ~~Cohort 7: (up to ~19 patients): Patients with a histologically confirmed stage IB-IIIA NSCLC and a *RET* fusion; determined to be medically operable and tumor deemed~~

~~resectable by a thoracic surgical oncologist, without prior systemic treatment for NSCLC. Cohort 7 is described in a separate addendum to this protocol.~~

3.6. Phase 2

~~Cohort 7 (up to ~19 patients): Patients with a histologically confirmed stage IB-IIIA NSCLC and a RET fusion; determined to be medically operable and tumor deemed resectable by a thoracic surgical oncologist, without prior systemic treatment for NSCLC.~~

4.1. Inclusion Criteria for Phase 1

For patients in Germany: Only adult patients capable of understanding the nature, significance and consequences of the clinical trial and providing informed consent are eligible for participation in the planned clinical trial.

4.2. Inclusion Criteria for Phase 2

~~Cohort 7: Patients with a histologically confirmed stage IB-IIIA NSCLC and a *RET* fusion; determined to be medically operable and tumor deemed resectable by a thoracic surgical oncologist, without prior systemic treatment for NSCLC. Cohort 7 is described in a separate addendum to this protocol.~~

4.3. Exclusion Criteria for Phase 1 and Phase 2

~~16. Phase 2 Cohort 7 (neoadjuvant treatment): Patient must not have received prior systemic therapy for NSCLC.~~

6.4. Removal of Patients from Therapy or Assessment

- Unacceptable toxicity
  Note: In Germany, this must be due to > Grade 3 or intolerable Grade 2 adverse event by CTCAE 4.3 considered related to study drug and despite protocol-allowed dose reduction

7. TESTS AND EVALUATIONS

~~Patients who are tolerating selpercatinib may have a reduced in-clinic visit assessment schedule after 6 months on treatment as described in Table 7-1. From Cycle 7 and onward, patients will be required to return to the clinic for in-person visits only during cycles where radiographic disease assessments are required, and for EOT and SFU visits. During non-disease assessment cycles, patients may continue to return for in person visits or may opt to have routine laboratory tests (e.g., serum chemistries, hematology, and liver function tests) completed at local healthcare facilities in conjunction with a telemedicine visit (telephone or equivalent). During the remote assessment, the site will perform an ECOG assessment, an AE assessment including whether the patient is experiencing any new, or changes to existing, AEs/SAEs and concomitant medications,~~

~~and will confirm study drug compliance and record missed doses. Patient responses during telemedicine visits will be recorded in source documents and results from any local assessments must be provided to the site for data entry into EDC.~~ Patients who are on selpercatinib treatment for at least 2 years will be required to return to the clinic for in-person visits only during cycles where radiographic disease assessments are required, and for EOT and SFU visits. Routine laboratory tests and telemedicine visits are not required but should be performed as clinically indicated during non-disease assessment cycles.

~~Should telemedicine visits result in patient complaint or concern from the study Investigator, the patient should return to the study site or be seen by a local provider for further assessment(s).~~

Table 7-1: Schedule of Assessments

* ~~For Cycle 7 and beyond, patients may have laboratories (e.g., serum chemistries, hematology, liver function tests, and urinalysis) completed at the study site or at local healthcare facilities during non-disease assessment cycles. As a result of this reduced in-clinic visit assessment schedule, the Sponsor understands that certain assessments (e.g., physical examination, vital signs) may not be obtainable during visits at local healthcare facilities. Beyond Cycle 7, these assessments are optional during local, non-disease assessment cycles, but should be collected when the patient returns to the clinic for disease assessment cycles.~~ Patients who are on selpercatinib treatment for at least 2 years will be required to return to the clinic for in-person visits only during cycles where radiographic disease assessments are required, and for EOT and SFU visits. Routine laboratory tests and telemedicine visits are not required but should be performed as clinically indicated during non-disease assessment cycles.

b. For Cycle 7 and beyond, patients may attend clinic visits only during cycles where radiographic disease assessments are required (Cycle 7, 9, 11, 13, and then Q12W thereafter) if telemedicine visit can be completed along with locally obtained lab assessments. Not applicable for Germany.

z. Study sites will conduct a telemedicine visit when no in-clinic visit occurs to confirm whether the patient is experiencing any new, or changes to existing, AEs/SAEs and concomitant medications, and to confirm study drug compliance and missed doses. Not applicable for Germany.

cc. Only for patients with a diagnosis of MTC and diarrhea at baseline. For Cycle 7 and beyond, the patient should personally maintain bowel diary and discuss the diary with the site during ~~telemedicine~~ visits. The bowel diaries should be returned at the next in-clinic visit or provided to study site electronically.

8.3 Determination of Sample Size

Notwithstanding the statistical considerations above, if approved by the SRC, enrollment beyond the above sample sizes in each of Cohorts 1-5, will be allowed, in order to accommodate enrollment demand and allow for the characterization of AEs that may occur with low frequency. With a sample size of 150 patients, the probability of observing one or more instances of a specific AE within a cohort with a true incidence rate of 1% and 2% is 77.9% and 95.2%, respectively. With a sample size of 250 patients, the probability of observing one or more instances of a specific AE within a cohort with a true incidence rate of 1% and 2% is increased to 91.9% and 99.4%, respectively. The sample size for Cohort 1 was increased to ~250 to accommodate enrollment demand. Additional enrollment will also allow for the characterization of AEs that may occur with low frequency which would enhance knowledge of the safety profile of selpercatinib. Further, this cohort allows for the enrollment of patients with RET fusion-positive solid tumors other than NSCLC. While the enrollment demand for patients with RET

fusion-positive NSCLC has been adequate for statistical analysis, additional solid tumor types remain underrepresented and enrollment expansion allows for data capture in this population.

Appendix L Provisions for Changes in Study Conduct During Exceptional Circumstances

The changes to procedures described in this appendix are temporary measures intended to be used only during specific time periods as directed by the sponsor in partnership with the investigator. Please note that Appendix L does not apply to Germany and should any of the events described herein requiring mitigation of study procedures be required, these will only be implemented in Germany after approval of a substantial amendment.

Denmark

This section describes protocol changes applicable for participants in study sites in Denmark.

In Denmark, continued access to the investigational medicinal product is not possible as part of the clinical trial. If patients are experiencing clinical benefit with no undue risks at the time of study completion, as determined by the investigator, access to the investigational medicinal product will be provided through permitted alternate approaches if needed.

Appendix L Provisions for Changes in Study Conduct During Exceptional Circumstances

Implementation of this appendix

The changes to procedures described in this appendix are temporary measures intended to be used only during specific time periods as directed by the sponsor in partnership with the investigator.

Exceptional circumstances

Exceptional circumstances are rare events that may cause disruptions to the conduct of the study. Examples include pandemics or natural disasters. These disruptions may limit the ability of the investigators, participants, or both to attend on-site visits or to conduct planned study procedures.

Implementing changes under exceptional circumstances

In an exceptional circumstance, after receiving the sponsor's written approval, sites may implement changes if permitted by local regulations.

After approval by local Ethical Review Boards, regulatory bodies and any other relevant local authorities, implementation of these exceptional circumstance changes will not typically require additional notification to these groups, unless they have specific requirements in which notification is required (for example, upon implementation and suspension of changes). All approvals and notifications must be retained in the study records.

If the sponsor grants written approval for changes in study conduct, the sponsor will also provide additional written guidance, if needed.

Considerations for making a change

The prevailing consideration for making a change is ensuring the safety of study participants. Additional important considerations for making a change are compliance with Good Clinical Practice, enabling participants to continue safely in the study and maintaining the integrity of the study.

Informed consent

Additional consent from the participant will be obtained, if required, for:

- participation in remote visits, as defined in Section "Remote Visits,"
- a change in the method of study intervention administration,
- dispensation of additional study intervention during an extended treatment period,
- alternate delivery of study intervention and ancillary supplies, and
- provision of their personal or medical information required prior to implementation of these activities.

Changes in study conduct during exceptional circumstances

Changes in study conduct not described in this appendix, or not consistent with applicable local regulations, are not allowed.

The following changes in study conduct will not be considered protocol deviations.

Remote visits

Types of remote visits

In source documents and the electronic Case Report Form (eCRF), the study site should capture the visit location and the method (e.g., telemedicine, mobile healthcare, etc.), with a specific explanation that includes the term 'COVID-19 related' (when applicable) for any data missing because of missed in-person site visits.

> **Telemedicine**: Telephone or technology-assisted virtual visits, or both, are acceptable to complete appropriate assessments. Assessments to be completed in this manner include, but are not limited to, concomitant medications, review of systems, Eastern Cooperative Oncology Group (ECOG) performance status (PS), dosing information, patient reported outcome measures, and information regarding local healthcare utilization/hospitalization.
>
> **Mobile healthcare:** Healthcare visits may be performed by a mobile healthcare provider at locations other than the study site when patients cannot travel to the site due to an exceptional circumstance if written approval is provided by the Sponsor. Procedures performed at such visits include, but are not limited to, review of systems, physical examinations, and laboratory studies (e.g., hematology, chemistry, etc.).
>
> **Other alternative locations**: Other procedures that may be done at an alternative location in exceptional circumstances include, but are not limited to, review of systems, physical examination, electrocardiogram (ECG) tracings, laboratory studies (e.g., hematology, chemistry), and radiologic imaging.

Regardless of the type of remote visits implemented, the protocol requirements regarding the reporting of adverse events (AEs), serious adverse events (SAEs), and product complaints remain unchanged. Furthermore, every effort should be made to enable patients to return to on-site visits as soon as reasonably possible, while ensuring the safety of both the patients and the site staff.

Local laboratory testing option

Local laboratory testing may be conducted in lieu of central laboratory testing. The local laboratory must be qualified in accordance with applicable local regulations.

Study intervention and ancillary supplies (including participant diaries)

When a participant is unable to go to the site to receive study supplies (including study drug) during normal on-site visits, the site should work with the sponsor to determine appropriate actions. These actions may include:

- asking the participant to go to the site and receive study supplies from site staff without completion of a full study visit,
- asking the participant's designee to go to the site and receive study supplies on a participant's behalf, and
- arranging delivery of study supplies.

These requirements must be met before action is taken:

- Alternate delivery of study intervention should be performed in a manner that does not compromise treatment blinding and ensures product integrity. The existing protocol requirements for product accountability remain unchanged, including verification of participant's receipt of study supplies.
- When delivering supplies to a location other than the study site (for example, participant's home), the investigator, sponsor, or both should ensure oversight of the shipping process to ensure accountability and product quality (that is, storage conditions maintained and intact packaging upon receipt).
- Instructions may be provided to the participant or designee on the final disposition of any unused or completed study supplies.

Documentation

Changes to study conduct will be documented

Sites will identify and document the details of how participants, visits types, and conducted activities were affected by exceptional circumstances. Dispensing/shipment records of study intervention and relevant communications, including delegation, should be filed with site study records.

Source documents at alternate locations

Source documents generated at a location other than the study site should be part of the investigator's source documentation and should be transferred to the site in a secure and timely manner.

Appendix M Protocol Amendment History

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

Amendment [11.0]

This amendment is considered to be substantial.

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

- safety or the rights of the study participants, and
- reliability and robustness of the data generated in the clinical study.

Overall Rationale for the Amendment:

The purpose of this amendment is provided in the table below.

Section # and Name	Description of Change	Brief Rationale
Synopsis	Updated to match changes in the main protocol	Alignment with main protocol updates
Section 1.7 Clinical Experience; Section 1.7.1. Known and Anticipated Risks	Updated data and simplified list of AEs of special interest	Update
Section 3.1 Study Design	Sentence added in regard to In Vitro Diagnostic Regulation	Update
Section 3.2.1. Length of Study	Added language regarding end of study and continued access	Update to study design

Section # and Name	Description of Change	Brief Rationale
Section 3.2.1 Length of Study and Section 3.4 Phase 1 and Maximum Tolerated Dose Determination; Section 3.7 Definition of RET Alterations; Table 3-3 Definition of RET Alterations; Section 4.1. Inclusion Criteria for Phase 1	Added statement regarding *RET* alteration result should be generated as per local guidelines including but not limited to IVDR compliance as applicable	To comply with the IVDR and ensure that *RET* testing meets EU clinical laboratory requirements
Section 3.2.2. End of Study	Added language regarding continued access follow-up	Update to study design
Section 3.6 Phase 2; Section 4.2 Inclusion Criteria for Phase 2; Section 4.3. Exclusion Criteria for Phase 2	• Removed Cohort 7 wording • Deleted exclusion criterion 16	• Align with leadership decision to end enrolment to most populations and remove cohort 7
Section 3.6. Phase 2; Figure 3-1 Study Schema	• Updated total number of patients and cohort patient distribution • Excluded Germany from Cohort 2 and 4 • Deleted language regarding Cohort 8 wording • Updated language regarding cycle length • Updated study schema	• Align with leadership decision to end enrolment to most populations and remove cohort 7 • Clarification • Correction • Update
Section 3.8. Number of Patients	• Updated total number of patients from 950 to 875	Align with leadership decision to end enrolment to most populations and remove cohort 7

Section # and Name	Description of Change	Brief Rationale
Section 4.1. Inclusion Criteria for Phase 1	• Updated inclusion criterion 13: birth control duration changed from 3 months to 1 month • Moved inclusion criterion 14 to Appendix K: Country-specific Requirement	• To align with label • For harmonization of the protocol and to avoid country and region-specific protocol versions in the EU
Section 6.1. Investigational Product	• Simplified language regarding selpercatinib provision	Clarification
Section 6.3.2. Allowed Concomitant Medications	• Clarified language regarding dose restriction for administration routes for systemic glucocorticoids	
Section 6.4. Removal of Patients from Therapy or Assessment	• Remove requirement for additional consultation/approval of post progression continuation (2nd or further PD) • Moved note for Germany into Appendix K: Country-specific Requirements	• Per new requirements • For harmonization of the protocol and to avoid country and region-specific protocol versions in the EU
Table 7-1 Schedule of Assessments; Section 7.3. Cycles 2 and Higher	• 12-lead ECG: added language in Cycle 7 column regarding ECG assessments until cycle 26 and beyond as clinically indicated; updated footnote “j”.	Clarification

Section # and Name	Description of Change	Brief Rationale
Table 7-1 Schedule of Assessments; Section 7.3 Cycles 2 and Higher	• Clarified that Urinalysis will be conducted "as clinically indicated" beyond C1D15; updated footnote "q"	Clarification
Table 7-1 Schedule of Assessments; Section 7.3. Cycles 2 and Higher; Section 7.8.5.3. Blood Biomarkers	• Whole blood for cfDNA analysis: updated number of collections; updated footnote "u"	To reduce the burden on patients.
Table 7-1 Schedule of Assessments; Section 7.3. Cycles 2 and Higher	• Updated language in Cycle 7-higher column	To align with local standard-of-care
Section 7.8.5.3. Blood Biomarkers	• Added language on use of samples	Addition
Section 7.8.5.4 Biomarker Samples	• Added section	Clarification on use of biomarker samples
Section 7.9. Continued Access	• Added section	Update to study design
Section 8.2.1. Safety Analysis Set	• Deleted statement regarding efficacy analysis	Clarification
Section 8.3. Determination of Sample Size	• Deleted language regarding exploring efficacy in patients with oncogenic drivers	Correction

Section # and Name	Description of Change	Brief Rationale
Section 8.5.1. Demographics and Baseline Characteristics; Section 8.5.2. Safety Analyses	• Clarified that patients will be tabulated, and safety analyses will be presented by tumor indication	Clarification
Section 8.5.3. Efficacy Analyses	• Updated language; added reference to SAP	Update
Section 8.5.4. Pharmacokinetic Analyses	• Updated language to match with Synopsis	Correction
Section 9.1. Safety Review Committee	• Clarified that Phase 2 safety committee will convene every 6 months for the first 5 years, and then annually • Removed language regarding additional SRC meetings after every fifth patient between ages 12 and 17	Aligned with Safety Steering Committee
Appendix K: Country-specific Requirements	• Added new section to capture protocol changes applicable for participants in study sites in Germany	Addition
Appendix L: Provisions for Changes in Study Conduct During Exceptional Circumstances	• Added new section to capture provisions for changes in study conduct during exceptional circumstances	Addition

Section # and Name	Description of Change	Brief Rationale
Appendix M: Protocol Amendment History	• Added new section to capture amendment history	Addition
Throughout	Minor editorial and document formatting revisions.	These are minor changes; therefore, they have not been summarized

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