Protocol: J2G-OX-JZJJ

A Phase 1/2 Study of the Oral RET Inhibitor LOXO-292 in Pediatric Patients with Advanced RET-Altered Solid or Primary Central Nervous System Tumors

NCT03899792

Approval Date: 21-Feb-2025

CLINICAL PROTOCOL LOXO-RET-18036 (J2G-OX-JZJJ)

A Phase 1/2 Study of the Oral RET Inhibitor LOXO-292 in Pediatric Patients with Advanced RET-Altered Solid or Primary Central Nervous System Tumors

Investigational Product:	Selpercatinib (LY3527723)
Protocol Number:	LOXO-RET-18036 (J2G-OX-JZJJ)
IND #:	142299
EudraCT #:	2019-000212-28
EU trial #:	2023-507703-63-00
Development Phase:	1/2
Sponsor:	Loxo Oncology, Inc., a wholly owned subsidiary of Eli Lilly and Company

Approval Date: Protocol Amendment 11 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 10.0	*09 October 2024*
Version 9.0	*15 August 2023*
Version 8.0	*30 June 2023*
Version 7.0	*21 December 2022*
Version 6.0	*19 May 2021*
Version 5.0	*05 October 2020*
Version 4.0	*19 December 2019*
Version 3.0	*02 August 2019*
Version 2.0	*11 January 2019*
Version 1.0	*09 November 2018*

Amendment [11]

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

Overall Rationale for the Amendment:

The purpose of this amendment is to update Appendix M to adjust the frequency of clinic visits and include remote visits in Spain and France.

Section # and Name	Description of Change	Brief Rationale
Appendix K Continued Access	Included footnote b Added footnote for remote visits. Minor editorial update.	Correction Alignment with Appendix M.
Appendix M Country-specific Requirements	Updated the frequency of clinic visits and added remote visits in Spain and France.	To reduce the burden on patients/align with the standard of care.

PROTOCOL SYNOPSIS

TITLE:

A Phase 1/2 Study of the Oral RET Inhibitor LOXO-292 in Pediatric Patients with Advanced RET-Altered Solid or Primary Central Nervous System Tumors.

PROTOCOL NUMBER:

LOXO-RET-18036 (J2G-OX-JZJJ)

EudraCT #: 2019-000212-28

EU trial #: 2023-507703-63-00

STUDY SITES:

Approximately 25 institutions will be recruited for participation in this study.

PHASE:

1/2

OBJECTIVES:

Study objectives are outlined below for Phase 1 and for Phase 2.

PHASE 1 Objectives

The objectives for the Phase 1 patient population (pediatric patients with advanced cancer harboring an activating RET alteration) are as follows:

Primary

The primary objective is to determine the safety, including dose-limiting toxicities (DLTs), of the oral RET inhibitor selpercatinib.

Secondary

- To characterize the pharmacokinetic (PK) properties of selpercatinib
- To identify the maximum tolerated dose (MTD) and/or the appropriate dose of selpercatinib for further clinical investigation
- ORR and CBR based on RECIST 1.1 or RANO as appropriate to tumor type as determined by an IRC and treating investigator

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- [redacted]
- [redacted]
- [redacted]
- [redacted]

PHASE 2 Objectives

The objectives for the Phase 2 patient population (pediatric patients with advanced cancer harboring an activating RET alteration) are as follows:

Primary

To determine the objective response rate (ORR) as determined by an Independent Review Committee (IRC) and measured by the proportion of patients with best overall confirmed response of complete response (CR) or partial response (PR) by Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST v1.1), or

Response Assessment in Neuro-Oncology (RANO) criteria, as appropriate, following treatment with selpercatinib.

Secondary

- To determine the following:
  - ORR based on the treating Investigator's response assessment using RECIST v1.1 or RANO criteria, as appropriate to tumor type
  - Duration of response (DOR) in patients with best overall response of CR or PR as determined by 1) an IRC and 2) the treating Investigator
  - Duration of progression-free survival (PFS) following initiation of selpercatinib by 1) an IRC and 2) the treating Investigator
  - Overall survival (OS) following initiation of selpercatinib
  - The clinical benefit rate (CBR) based on the proportion of patients with best overall response of CR, PR, or stable disease (SD) lasting 16 or more weeks following initiation of selpercatinib as determined by 1) an IRC and 2) the treating Investigator
- To assess the safety profile and tolerability of selpercatinib
- To characterize the PK properties of selpercatinib in pediatric patients
- To evaluate the concordance of prior molecular profiling that detected an activating RET alteration within the patient's tumor with diagnostic test(s) being evaluated by the Sponsor
- To characterize post-operative staging and surgical margin status in patients who have definitive surgery following treatment with selpercatinib
- To evaluate change from baseline in patient-reported pain at BOR visit as assessed by the Wong-Baker Faces Scale
- To assess the acceptability and palatability of selpercatinib CCI in patients under age 18.

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STUDY DESIGN:

Phase 1 Dose Escalation

This is a multicenter, open-label, Phase 1/2 study in pediatric patients with an advanced solid or primary CNS tumor harboring an activating RET alteration. Selpercatinib will be administered orally twice daily (BID), with the dose adjusted by body surface area (BSA).

The starting dose level is intended to deliver equivalent exposure to the recommended Phase 2 dose (RP2D) in CCI. Planned dose levels are listed in Table 3-1. Body surface area (BSA) will be determined by the Mosteller (√((height × weight)/3600)) (Mosteller 1987). Doses for each cohort will be increased incrementally until an MTD or RP2D is reached. The maximum dose (regardless of BSA calculation) will be no higher than the recommended adult dose associated with the BSA-based dosing, i.e., patients in Dose Cohort 1 will receive a dose no higher than 160 mg BID.

This trial will use a CCI Dose Escalation CCI

CCI patients will be enrolled in each dose cohort, also referred to as dose levels. Each patient will participate in only 1 dose cohort. The total number of patients to be enrolled in the dose escalation phase 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. Each dose level in the dose escalation portion will enroll no more than 15 patients.

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.

Each patient in a given cohort must have completed safety assessments through Cycle 1, Day 28, and received a minimum of 75% of the planned total dose in Cycle 1 (unless due to toxicity) to be eligible for the assessment of DLT. CCI If no DLT then accrual in the next highest cohort will begin immediately. If the first 3 patients have not cleared the DLT window, additional patients may be enrolled on the current dose level up to a maximum of [redacted]. A minimum of [redacted] patients in a given cohort must have completed 28 days of safety assessment in Cycle 1 without DLT and a maximum of CCI in [redacted] patients who have completed the DLT window before the next cohort initiates accrual. Escalation will proceed through the [redacted] dose levels until the MTD or RP2D is reached. Based on the interim evaluation of the safety and tolerability data of the previous cohort, it may be decided to enroll additional patients in a previously studied cohort or at an intermediate dose level.

If CCI patients within a cohort experience a DLT, then the dose escalation will stop. In order for the MTD/RP2D, the Safety Review Committee (SRC) will evaluate whether the previous lower dose level will be considered the MTD (Table 3-1 shows example doses), whether an intermediate dose level should be evaluated, and/or whether additional patients need to be evaluated if the DLTs seen at this dose level are considered to be not serious or equivocal with regard to causal relationship to selpercatinib.

Patients are eligible for intra-patient dose escalation to the highest dose cohort that has been determined safe. However, intra-patient dose escalation is not required; it is only appropriate if the treating Investigator and Sponsor believe it is in the best interest of the patient.

Escalation will proceed through the planned dose levels, or until the MTD is reached, or until the Sponsor determines that a suitable dose has been achieved based on PK exposure and toxicity.

Dose-Limiting Toxicity Definition

A DLT is defined as any of the following treatment-emergent adverse events (TEAEs; a TEAE is defined as an adverse event [AE] that starts on or after the first administration of study drug) occurring in the first 28 days (i.e., in Cycle 1), and not reasonably attributed to patient's underlying disease or other medical condition and deemed by the Investigator to be related to selpercatinib as assessed via CTCAE v5.0:

- Any Grade 3 or higher nonhematologic toxicity, with the exception of Grade 3 fatigue, nausea, tendon reflex decrease, or weight gain attributable to normal growth and development
- Grade 3 vomiting or diarrhea will be considered DLT only if it persists for > 48 hours despite standard of care treatment. Admission to the hospital of patients < 1 year of age with Grade 3 vomiting or diarrhea is recommended until these events resolve to Grade 1.

Grade 4 vomiting or diarrhea will be considered DLT regardless of duration. Admission to the hospital of patients < 1 year of age with Grade 4 vomiting or diarrhea is recommended until these events resolve to Grade 1.

Any toxicity, regardless of the Common Terminology Criteria for Adverse Events (CTCAE) grade, resulting in discontinuation or dose reduction of treatment (with the exception of symptoms related to disease progression [PD])

Grade 4 thrombocytopenia or Grade 3 thrombocytopenia with Grade 1 or higher bleeding

Grade 4 anemia lasting > 8 days, despite supportive therapy, not explained by underlying condition (transfusions are allowed during Cycle 1), and persists beyond the initial transfusion

Grade 4 neutropenia, lasting > 8 days, despite supportive therapy (Cycle 1 growth factor support not allowed for prophylaxis)

Grade 3 uncomplicated febrile neutropenia *will not* be considered a DLT

Phase 2 Expansion Cohorts

Additional patients may be enrolled to better characterize the safety and efficacy of the selpercatinib dose recommended for further study. Patients may enroll into each of the 4 cohorts below, depending on disease characteristics (refer to Synopsis Table 1).

Synopsis Table 1: Disease Criteria for Enrollment for Cohorts 1 to 4

Cohort	Disease Criteria
Cohort 1	RET fusion-positive solid tumor (excluding CNS primary) with measurable disease
Cohort 2	RET-mutant MTC with measurable disease
Cohort 3	RET fusion-positive primary CNS tumor with measurable disease
Cohort 4	Any patient with RET mutation/alteration not fitting Cohort 1 to 3 criteria (i.e., RET alterations via plasma cfDNA or non-CLIA certified test, non-measurable (i.e., only evaluable) disease

Abbreviations: cfDNA = circulating free DNA; CNS = central nervous system; MTC = medullary thyroid cancer.

ELIGIBILITY CRITERIA:

Inclusion Criteria

1. Pediatric patients 6 months of age and 21 years of age at Cycle 1 Day 1 (C1D1) with a locally advanced or metastatic solid or primary CNS tumor that has relapsed, progressed or was nonresponsive to available therapies and/or for which no standard or available systemic curative therapy exists.
    a) Patients with locally advanced disease who would require, in the opinion of the Investigator, disfiguring surgery, or limb amputation to achieve a complete surgical resection are also eligible.
    b) In geographies where a selective RET-inhibitor is approved, patients may enroll without prior systemic treatment.
2. Evidence of an activating *RET* gene alteration in tumor and/or blood (e.g., gene rearrangement and/or mutation, excluding synonymous, frameshift, or nonsense mutations) as identified through molecular assays, as performed for clinical evaluation.
    a) 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 in vitro diagnostic regulation (IVDR) compliance as applicable. In cases where such certification is not clearly demonstrated to determine eligibility, the Sponsor should be contacted to discuss laboratory test results.
    b) A positive germline test for a *RET* mutation is acceptable for patients with MTC.
    c) In addition to RET fusion-positive solid tumors and RET-mutant MTC, 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.

3. Patients with primary CNS tumors or cerebral metastasis:
    a) Must be neurologically stable based on stable neurologic exam for 7 days prior to enrollment
    b) Must have not required increasing doses of steroids within the 7 days prior to enrollment to manage CNS symptoms
4. Imaging study must be performed within 28 days of C1D1 while on stable dose steroid medication (if needed) for at least 7 days immediately before the imaging study.
5. Histologic verification of malignancy at original diagnosis or relapse, except in patients with intrinsic brain stem tumors, optic pathway gliomas, or patients with pineal tumors and elevations of cerebral spinal fluid (CSF) or serum tumor markers including alpha-fetoprotein or beta-human chorionic gonadotropin (HCG).
6. Must have measurable or non-measurable but evaluable disease.
7. Karnofsky (patients 16 years and older) or Lansky (patients younger than 16 years) performance score of at least 50.
8. Must have fully recovered from the acute toxic effects of all prior anti-cancer chemotherapy to CTCAE (v5.0) Grade 2.
    a) Myelosuppressive chemotherapy: Start of selpercatinib must be at least 21 days after the last dose of myelosuppressive chemotherapy (42 days if prior nitrosourea).
    b) Investigational agent or anticancer therapy other than chemotherapy: Not within 2 weeks prior to planned start of selpercatinib or 5 half-lives, whichever is shorter. Full recovery of clinically significant toxicities from that therapy must be evident. Prior MKIs with anti-RET activity are allowed. Refer to Appendix I for examples of MKIs with anti-RET activity. Patients who have previously received selpercatinib are not eligible.
    c) Radiation therapy (XRT): Start of selpercatinib must be at least 14 days after local palliative radiation (small port); at least 42 days must have elapsed before start of selpercatinib if other substantial bone marrow radiation, including prior radio-iodized metaiodobenzylguanidine (^{131}I-MIBG) therapy.
    d) Stem cell infusion (ASCT, Allogenic or CAR-T) without total body irradiation (TBI): No evidence of active graft versus host disease and at least 56 days must have elapsed before start of selpercatinib after transplant or stem cell infusion.
    e) Hematopoietic growth factors: Start of selpercatinib must be at least 14 days after the last dose of a long-acting growth factor (e.g., pegfilgrastim); or 7 days for short-acting growth factor.
9. An archival (FFPE or fresh frozen) or fresh tumor tissue sample must be available (refer to Section 7.5). If archival tumor tissue sample is not available, a fresh biopsy (at a primary or metastatic site) should be performed. If an archival or fresh sample cannot be obtained safely, the patient may still be eligible with documented Sponsor approval.
10. Adequate hematologic status, defined as:
    a) Qz „ ≥) ≥ –“;)•)4Qf S 5))A>) 10^9/L not requiring growth factor support for at least 7 days prior to treatment.
    b) h,y ≥,≥)•))GE) 10^9/L not requiring transfusion support for at least 7 days prior to treatment.
    c) Yz))H)× –≤d) not requiring transfusion support or erythropoietin for at least 7 days prior to treatment.
11. Adequate hepatic / pancreatic function, defined as:
    a) Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) 2.5 the upper limit of normal (ULN) or 5 ULN with documented liver involvement (such as liver metastasis or a primary biliary tumor), *and*
    b) Total bilirubin 1.5 ULN or 3 ULN with documented liver involvement)X“;z≥) Disease 4 y “≥) “–)X“;z≥)T“ ≥y ≥)× y)z≥)≥ „≥) “–) prior Sponsor approval).
12. Adequate renal function, defined as:
    a) U “× y ≥)–„ × ≥ ,y)√“„ y “) y ≥) 30 mL/min/1.73 m^2 based on local institutional practice for determination, or a maximum serum creatinine by age and gender as presented in Synopsis Table 2.

Synopsis Table 2: Serum Creatinine by Age and Gender

	Maximum Serum Creatinine (mg/dL)		Maximum Serum Creatinine (µmol/L)	
Age	**Male**	**Female**	**Male**	**Female**
6 months to < 1 year	0.5	0.5	44	44
1 to < 2 years	0.6	0.6	53	53
2 to < 6 years	0.8	0.8	71	71
6 to < 10 years	1	1	88	88
10 to < 13 years	1.2	1.2	106	106
13 to < 16 years	1.5	1.4	132	124
16 years	1.7	1.4	150	124

13. Ability to comply with outpatient treatment, laboratory monitoring, and required clinic visits for the duration of study participation.
14. Willingness of male and female patients with reproductive potential to utilize double effective birth control methods, defined as one used by the patient and another by his/her partner, for the duration of treatment and for 1 month following study completion.

    For male patients with a non-pregnant female partner of child-bearing potential, and women of child-bearing potential, one of the following highly effective birth control methods (with a failure rate of less than 1% per year when used consistently and correctly) are recommended:

    a) Combined estrogen and progestogen containing hormonal contraception associated with inhibition of ovulation given orally, intravaginally, or transdermally
    b) Progestin-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: considered a highly effective method only if defined as refraining from heterosexual intercourse during an entire period of risk associated with the study treatment. The reliability of sexual abstinence will be evaluated in relation to the duration of the study and to the usual lifestyle of the patient.

15. Ability to swallow capsules, liquid suspension, or gastric access via a naso- or gastric tube.

    The patient and, when applicable, the parent/guardian of child or adolescent patient has the ability to understand, agree to, and sign the study Informed Consent Form (ICF) and applicable Pediatric Assent Form before initiation of any protocol-related procedures; patient has the ability to give assent, as applicable, at the time of parental/guardian consent

16. [removed].

Exclusion Criteria

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

1. Major surgery within 2 weeks prior to C1D1.
2. Clinically significant active cardiovascular disease or history of myocardial infarction within 6 months prior to C1D1; ongoing cardiomyopathy; or current prolonged QT interval corrected for heart rate (QTc) " ≥ y,,)N)DD>)× ",,," ≥• ≤)√) y "≥))AE) ≥y) ,,≤)y ≤)N)DG>)× ",,," ≥• ≤)√) y "≥)N)AE) ≥y) ,,≤:)V) y "≥))AE) ≥y) ,,≤8)Ry ≥)V × ,,y) ",,,)z≥) ",,," ≥≤))≤≥ ≥ × " ≥)i 1 • :)V) y "≥)N)AE) years old, either method, Fridericia)Ry ≥)V × ,,y)× y)z≥)y ,,"≥≤:)

3. Active uncontrolled systemic bacterial, viral, or fungal infection, which in the opinion of the Investigator makes the risk: benefit ratio for the patient to participate in the trial unfavorable. Screening for chronic conditions is not required.
4. Clinically significant active malabsorption syndrome or other condition likely to affect gastrointestinal absorption of the study drug.
5. Pregnancy or lactation.
6. Uncontrolled hypotension or hypertension ≥ Grade 3 CTCAE (v5.0).
7. Uncontrolled symptomatic hyperthyroidism or hypothyroidism (i.e., the patient required a modification to current thyroid medication in the 7 days before start of selpercatinib).
8. Uncontrolled symptomatic hypercalcemia or hypocalcemia.
9. [Removed]
10. Known hypersensitivity to any of the components of the investigational agent, selpercatinib or Ora-Sweet® SF and OraPlus®, for patients who will receive selpercatinib suspension.
11. [Removed]
12. [Removed]

ETHICAL CONSIDERATIONS OF BENEFIT/RISK:

Pediatric patients with RET-fusion cancers (papillary thyroid, soft tissue sarcoma, others) and RET mutated cancer represent populations with high unmet need. The 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 to be favorable.

PLANNED SAMPLE SIZE:

In the Phase 1 portion of the study, a minimum of [redacted] patients will be enrolled into a dose escalation cohort. Over-enrollment (maximum of [redacted] patients per dose escalation cohort) may occur in the dose escalation cohorts as previously described above in *Phase 1 Dose Escalation*.

In the Phase 2 portion of the study, additional patients may be enrolled to better characterize the safety and efficacy of the selpercatinib RP2D. The Phase 2 portion will enroll approximately [redacted] patients into Cohorts 1 and 2. The total sample size for Phase 2 will not exceed [redacted].

INVESTIGATIONAL DRUG:

Selpercatinib will be provided as a liquid suspension, a capsule containing drug substance with a simple blend of excipients [redacted]. The capsules [redacted] will be provided to the sites for distribution to the patient for outpatient administration. Liquid suspension is provided to the pharmacy as powder and subsequently compounded [redacted]

TREATMENT PROCEDURES:

Patients will begin BID dosing on C1D1 according to the assigned cohort. Each cycle will consist of 28 days of continuous dosing; for patients who reach 2 years of study treatment, cycles may be extended to 84 days in length. Individual patients will continue dosing until PD, unacceptable toxicity, or other reason for treatment discontinuation. Patients with documented PD may be allowed to continue selpercatinib if the patient is tolerating treatment and, in the opinion of the Investigator and Sponsor, is deriving clinical benefit from continuing study medication. Four weeks after the last dose, all treated patients will undergo a safety follow-up visit.

STUDY ASSESSMENTS:

Safety assessments will be performed, including physical examination, body weight, Karnofsky (patients 16 years and older) or Lansky (patients younger than 16 years) performance score, clinical AEs, laboratory variables (hematology, serum chemistries, and urinalysis), electrocardiogram (ECG), vital signs, and thyroid function.

Efficacy assessments include tumor evaluation at regularly scheduled intervals. Investigators may elect to conduct an initial tumor evaluation on Cycle 2 Day 1 or a confirmatory tumor evaluation at an otherwise unscheduled visit, as permitted by local regulatory authority and IRB requirements. All scans will be collected and stored at a central facility to permit central reviewer assessment if desired. An End of Treatment (EOT) visit is required within 7 days of the last dose of selpercatinib or the decision to terminate study drug. In addition, a Safety Follow-up (SFU) visit 28 days (+7 days) after the last dose of study drug is required.

Finally, all patients will enter Long-Term Follow-Up (LTFU) (~every 3 months for up to 2 years) period of observation, for the purpose of confirming the resolution of any AEs, PD if not occurring on study, subsequent anticancer therapy(ies), and survival. LTFU may be conducted by phone. Patients who discontinue study drug for reasons other than disease progression, lost to follow-up, withdrawal of consent or initiation of a new anticancer therapy(ies), will continue undergoing disease assessment by imaging (as specified above; utilizing the same modality[ies] used for the baseline imaging assessment) until PD, withdrawal of consent, or initiation of a new anticancer therapy(ies).

Blood for PK assessment will be collected in accordance with Appendix B (and Table 11-2). If patients have an Ommaya Reservoir or undergo lumbar puncture (LP) during the time of study drug administration, CNS fluid will also be CCI

Pain and Quality of Life (QoL) Assessments will be collected every Cycle. Pain will be assessed by the Wong-Baker Faces Scale (http://wongbakerfaces.org) at every office visit. QoL will be assessed using the PedsQL-Cancer Module for both the patient and their parent/caregiver: (http://www.proqolid.org/instruments/pediatric_quality_of_life_inventory_cancer_module_pedsql_cancer_module) at every office visit.

ENDPOINTS:

Study endpoints are outlined below for Phase 1 and for Phase 2.

PHASE 1 Endpoints

Primary

Frequency, severity and relatedness of TEAEs and SAEs, including DLTs in pediatric patients receiving selpercatinib

Secondary

- 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}), maximum drug concentration (C_{max}), time to maximum plasma concentration (T_{max}), degree of accumulation, and other characterizations
- The MTD and/or the RP2D of selpercatinib in pediatric patients
- ORR and CBR based on RECIST 1.1 or RANO as appropriate to tumor type as determined by an IRC and treating investigator

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PHASE 2 Endpoints

Primary

ORR based on RECIST v1.1 or RANO as appropriate to tumor type as determined by an IRC

Secondary

- ORR based on RECIST v1.1 or RANO as appropriate to tumor type per the treating Investigator's response assessment
- DOR (IRC and treating investigator)
- PFS (IRC and treating investigator)
- OS
- CBR (IRC and treating investigator)
- 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}, T_{max}, degree of accumulation, and other characterizations
- The percent positive agreement between prior molecular profiling that detected a RET alteration within the patient's tumor and diagnostic test(s) being evaluated by the Sponsor
- Post-operative staging and surgical margin status in patients who have definitive surgery following treatment with selpercatinib
- Change from baseline in patient-reported pain at BOR visit as assessed by the Wong-Baker Faces Scale.
- Acceptability and palatability of selpercatinib CCI [redacted] in patients under age 18.

CCI [redacted]

STATISTICAL METHODS:

Safety Analyses

An SRC will be established to oversee the safety aspects of the study and to render dose escalation and RP2D or MTD decisions in the dose escalation portion of the study. Specifically, the Committee will perform ongoing review of serious adverse events (SAEs) and other safety trends throughout the conduct of the study. The Committee membership will consist of the Sponsor's representatives and clinically qualified individuals from each active clinical site. The Committee will be convened as needed and decisions will be documented in written minutes.

Safety analyses will be conducted using the Safety Analysis Set (SAS), which consists of all patients treated with at least 1 dose of study drug.

TEAEs reported during the study will be tabulated and listed by Sponsor Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) and Preferred Term (PT). Tables will display number and percentage of patients experiencing the event for the following categories: All AEs, AEs considered related to study drug, AEs by severity, DLTs, AEs occasioning treatment delay or discontinuation, and SAEs. For the dose escalation phase, the observed DLT rate in each dose cohort will be calculated by the proportion of patients who experienced DLT with a 2-sided 95% exact binomial confidence interval (CI).

Efficacy Analyses

The efficacy analyses will be conducted on Safety Analysis Set unless otherwise specified. The efficacy outcomes will be summarized by cohort or by tumor type as deemed appropriate.

ORR will be estimated using disease-specific response criteria (e.g., RECIST v1.1 for patients with solid tumor). 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. All responses will be confirmed by a second scan 28 days after the initial response. The estimate of the ORR will be accompanied by 2-sided 95% CIs. The primary analysis of ORR will be based on the responses determined by an IRC. A secondary analysis will be based on the treating Investigator s assessment of response.

Time-to-event endpoints (DOR, PFS and OS) will be summarized descriptively using the Kaplan-Meier method. The Kaplan-Meier estimate with 95% CI calculated using Brookmeyer and Crowley method will be provided for the median. The event-free rate with the 95% CI calculated using X ≥≥ ≤)√ × ,y) “,,z≥) “≍)√) selected time points. Median follow-up for each endpoint will be estimated according to the Kaplan Meier estimate of potential follow-up.

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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
ACTH	adrenocorticotropic hormone
AE	adverse event
AIEOP-STSC	Associazione Italiana Ematologia Oncologia Pediatrica Soft Tissue Sarcoma Committee
AKT	protein kinase B
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ASCO	American Society for Clinical Oncology
AST	aspartate aminotransferase
ATP	adenosine triphosphate
AUC	area under the concentration versus time curve
AUC_{0-12}	area under the curve time 0 to 12 hours
AUC_{0-24}	area under the curve time 0 to 24 hours
AUC_{0-t}	area under the concentration versus time curve from time 0 to t
BDNF	brain-derived neurotrophic factor
BCRP	breast cancer resistance protein
BID	twice daily
BUN	blood urea nitrogen
BSA	body surface area
C	Cycle
C1D1	Cycle 1 Day 1
CBR	clinical benefit rate
CDMS	Clinical Database Management System
CEA	carcinoembryonic antigen
cfDNA	circulating free DNA
CI	confidence interval
CIPA	congenital insensitivity to pain with anhidrosis
CL/F	apparent oral clearance of drug
CLIA	Clinical Laboratory Improvement Amendments
C_{max}	maximum drug concentration
C_{min}	trough drug concentration
CMN	congenital mesoblastic nephroma tumors
CNS	central nervous system
COPD	chronic obstructive pulmonary disease

Abbreviation or term	Definition
CR	complete response
CRF	Case Report Form
CSF	cerebral spinal fluid
CT	computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
CYP3A4	cytochrome P450 3A4
D	Day
DD	dimerization domain
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DOR	duration of response
ECG	electrocardiogram
eCRF	electronic Case Report Form
EDC	electronic data capture
EIAEDs	enzyme-inducing anti-epileptic drugs
ENS	enteric nervous system
EOT	end of treatment
ERK	extracellular signal-related kinases
ETV6	ETS variant gene 6
FACES	Wong-Baker Faces Scale
FDA	Food and Drug Administration
FGFR	fibroblast growth factor receptor
FISH	fluorescence in situ hybridization
FLAIR/T2	T2-weighted fluid-attenuated inversion recovery
FOB	functional observational behavioral
GAB1	GRB2-associated-binding protein 1
GALT	gut-associated lymphoid tissue
GCP	Good Clinical Practices
GDNF	glial cell line-derived neurotrophic factor
GDPR	EU General Data Protection Regulation
GFLs	glial cell line-derived neurotrophic factor family ligands
GI	gastrointestinal
GIT	gastrointestinal tract
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GPI	glycosylphosphatidylinositol

Abbreviation or term	Definition
GRB2	growth factor receptor-bound protein 2
H	hour
Hb	hemoglobin
HCG	human chorionic gonadotropin
HED	human equivalent dose
hERG	human ether-à-go-go related gene
HP- -CD	hydroxypropyl-beta-cyclodextrin
HREC	Human Research Ethics Board
HRQoL	Health Related Quality of Life
HSA	human serum albumin
^{131}I-MIBG	radio iodized metaiodobenzylguanidine
IB	a ≥ “–y)R •— ≥
IC_{50}	concentration at which 50% inhibition is achieved
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IFS	infantile fibrosarcoma
IHC	immunohistochemistry
IM	infantile myofibromatosis
IMP	Investigational Medicinal Product A medicinal product which is being tested or used as a reference, including as a placebo, in a clinical trial.
IMT	infantile myofibroblastic tumors
IRB	Institutional Review Board
IRC	Independent Review Committee
IRS	insulin receptor substrate OR Intergroup Rhabdomyosarcoma Staging
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IVRS	interactive voice response system
KD	kinase domain
LDH	lactate dehydrogenase
LMA	locomotor activity assessments
LP	lumbar puncture
LTFU	Long-term Follow-up
MAP	mitogen-activated protein
MAPK	mitogen-activated protein kinase
MASC	mammary analogue secretory carcinoma

Abbreviation or term	Definition
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 “——) √)× ≍“•y “) ≥J) –≥) “——) y “•“ y 8) –≥) “——)≤ –8) –≥) “——)≤ ≥8) “——) route, at the right time. In addition to the core five rights, the following may also represent medication errors:)≤ ≥) ×“ “)y •“y ≍) “–)y)QU))y) ≤ •)• × „y“)≤“ ≥ “ –)) ≥) √)≥ “≍)× ≍“•y “) ≥) √)× ≍“•y “) y) –≥) ≥• × × ≥ ≍≍)“ -use date)≤“ ≥ “ –)) ≥) √)y)“× ≥ „) ≍)× ≍“•y “) ≥) √)y)y≤ „≥ y ≍)≤ yge form or administration technique inconsistent with the medication's labeling (for example, Summary of Product Characteristics, IB, local label, protocol), or) –y ≍) ≥) √)• y “≤–≥ 8) ≥√‘„≍) ≥ 8))z –÷
MEK	mitogen-activated protein kinase
MIBG	meta-iodobenzylguanidine scans
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
MKI	multikinase inhibitor
MRI	magnetic resonance imaging
MRSD	maximum recommended starting dose
MTC	medullary thyroid cancer
MTD	maximum tolerated dose
MYCN	myelocytomatosis viral-related oncogene
NA	not applicable
NCI	National Cancer Institute
NSCLC	non-small cell lung cancer
NGF	nerve growth factor
NGS	next generation sequencing
NOAEL	no-observable-adverse-effect-level
NT-3, -4, -5	neurotrophin-3, -4, -5
NTRK genes	neurotrophic tyrosine kinase receptor genes
NTRK1, -2, -3	human neurotrophic tyrosine kinase receptor gene or mRNA, types 1, 2, and 3, coding for TRKA, TRKB, and TRKC, respectively
ORR	objective response rate
OS	overall survival
PD	progressive disease or disease progression
PDX	patient-derived xenografts

Abbreviation or term	Definition
PedsQL-Core	Pediatrics Quality of Life - Core Module
PET	positron emission tomography
PFS	progression-free survival
P-gp	P-glycoprotein
Ph+	Philadelphia chromosome positive
PI3K	Phosphoinositide 3-phosphate
PK	pharmacokinetic
PNS	peripheral nervous system
PO	*per os*, orally
PPI	proton pump inhibitor
PR	partial response
PT	prothrombin time *or* preferred term
PTC	papillary thyroid cancers
PTT	partial thromboplastin time
QD	once daily
QoL	quality of life
QTc	QT interval corrected for heart rate
RAF	raf kinase
RANO	Response Assessment in Neuro-Oncology (RANO) Criteria
RAS	ras protein
RBC	red blood cell(s)
REB	Research Ethics Board
RECIST v1.1	Response Evaluation Criteria in Solid Tumors version 1.1
RNA	ribonucleic acid
RP2D	recommended Phase 2 dose
RTK	receptor tyrosine kinase
RT-PCR	reverse transcription polymerase chain reaction
SAE	serious adverse event
SAS	Safety Analysis Set
SBC	secretory breast cancer
SD	stable disease *or* standard deviation
SEER	Survey of Epidemiology and End Results
SFU	Safety Follow-up
SGPT	serum glutamic-pyruvic transaminase
SHC	Src Homology 2 Domain Containing Transforming Protein
SIOP-MMT	International Society of Pediatric Oncology Malignant Mesenchymal Tumor Committee
SOC	system organ class

Abbreviation or term	Definition
SOS	son of Sevenless protein
SRC	Safety Review Committee
STD_{10}	severely toxic dose in 10% of animals
STSs	soft tissue sarcomas
SUSAR	suspected unexpected serious adverse reaction 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.
$T_{1/2}$	half-life
TBI	total body irradiation
TEAE	treatment-emergent adverse event (a TEAE is defined as an AE that starts on or after the first administration of study medication)
TKI	tyrosine kinase inhibitor
T_{max}	time to maximum plasma concentration
TRK	tropomyosin-related kinase
TTE	time-to-event
Tyr	phosphorylated tyrosine
ULN	upper limit of normal
US	United States
VA	vincristine plus actinomycin-D
V/F	volume of distribution
V_z/F	apparent oral volume of distribution
UICC	Union for International Cancer Control
WBC	white blood cell(s)
WHO	World Health Organization
XRT	X-ray therapy

1 INTRODUCTION

1.1 RET Gene and Receptor/Normal RET

RET is a receptor tyrosine kinase (RTK) with critical roles in normal organogenesis and in the maintenance of several tissue types, including neural, neuroendocrine, hematopoietic and male germ cell (Mulligan 2014).

During embryogenesis, RET is expressed in the excretory and parasympathetic nervous systems. In the nervous system, RET is expressed in the progenitors of the enteric nervous system (ENS), in the enteric, autonomic, and sensory neurons of the peripheral nervous system (PNS), and in the motor and catecholaminergic neurons of the central nervous system (CNS). RET-homozygous mice have severe hypodysplasia or anaplasia of the kidneys. C-RET is also required for the development of the ENS. C-RET-homozygous mice lack all enteric ganglia posterior to the stomach. In humans, mutations of RET ≥ „)“)Y“ •— –)≤“ ≥y ≥:)

RET is the signaling component of multi-subunit receptor complexes for glial cell line-derived neurotrophic factor (GDNF) family ligands (GFLs), which belong to the TGF-beta superfamily (Baloh et al. 2000; Saarma 2000). The interaction between the GFLs and RET is mediated by glycosylphosphatidylinositol (GPI)-linked cell-surface glycoproteins, called GFR alpha 1 4 (Airaksinen et al. 1999). Among the signaling pathways activated by RET are the MAP kinase (MAPK) and the PI3-K pathway (van Weering and Bos 1998). As is the case for other RTKs, phosphorylated tyrosine (Tyr) residues in RET are critical for the formation of docking sites for intracellular adaptor and effector signaling molecules (de Graaff et al. 2001).

1.2 Tumors with RET Abnormalities and Current Treatment Options

Genetic alterations in the *RET* gene are implicated in the pathogenesis of several human cancers affecting both adult and pediatric patient populations. *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 medullary thyroid cancer (> 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).

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 medullary thyroid cancer (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 (Chuk et al, 2018). 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).

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.

1.3 Role of RET in Pediatric Cancers

The application of next-generation sequencing (NGS) approaches to a large collection of human tumors has led to the identification of *RET* gene in a fraction of other tumor types, including infantile myofibromatosis (IM), infantile fibrosarcoma, 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).

The high-frequency alterations in a less-prevalent cancer like MTC and the potential additional role of RET in other rare and/or pediatric cancers indicates that a significant number of patients with advanced, RET-fusion and/or RET-mutant cancers could benefit from potent and selective RET kinase inhibition.

Available evidence indicates that 7 to 10% of all thyroid malignancies occur in children and young adults. Hereditary MTC syndromes are present in almost all children and young adults diagnosed with MTC and are known to be caused by missense mutation in the RET proto-oncogene. Standard of care treatment for non-metastatic MTC in young patients is total thyroidectomy, which is associated with long-term sequelae of hypothyroidism and the need for continuous thyroid hormone replacement. Patients with a family history of hereditary MTC, harboring a germline RET mutation are treated with prophylactic total thyroidectomy after reaching the age of 5 in an effort to prevent the development of MTC. Anti-RET multikinase inhibitors cabozantinib and vandetanib have proven anti-tumor activity in adult patients with MTC and have demonstrated preliminary anti-tumor activity in young children with MTC (Fox et al. 2013).

Case reports of patients with IM and infantile myofibroblastic tumors (IMT) indicate that RET mutations may be a primary oncogenic driver for a subset of these cancers. There have been no clinical trials due to the rarity of these diseases, and most treatment approaches have been published as single case reports. The most common therapeutic intervention is surgery, although this is not a viable option for many patients due to tumor location. Additionally, patients with IM or IMT may receive cytotoxic chemotherapy typically including an alkylating agent. These regimens (such as vincristine, actinomycin-D and cyclophosphamide) are not well tolerated and lead to side effects including pain, neuropathy, infection, renal/hepatic dysfunction, cardiac toxicity, delayed achievement of growth and neurologic milestones, infertility, and secondary malignancies. Given the short and long-term toxicities associated with multiagent chemotherapy, there is a need for effective targeted therapies with improved short-term and long-term toxicity profiles in pediatric patients with IM and IMT (Rosenzweig et al. 2016).

Cabozantinib and vandetanib, small molecule inhibitors of multiple kinases including RET, have been approved for adults with advanced, progressive and/or symptomatic MTC (Fox et al. 2013). Many patients require dose reduction due to significant toxicities. A Phase 1/2 clinical trial of vandetanib in 12 pediatric or adolescent patients with MTC demonstrated an objective response rate of 47% with diarrhea as the most common dose-limiting toxicity (DLT). Recently, cabozantinib was studied in a Phase 1 dose escalation pediatric study. While the authors reported that a maximum tolerated dose (MTD) was not reached, 3 patients discontinued therapy due to DLTs. While the study was conducted as an all-comer population study, 2 patients with MTC achieved partial responses (PRs). All patients with MTC had a decrease in calcitonin within the first cycle (Chuk et, al. 2018).

Patients with RET fusion-positive cancers (IM, congenital mesoblastic nephroma tumors [CMN], thyroid, and others) and RET-mutated cancers (MTC) represent populations with high unmet clinical need. In IM and CMN, chemotherapy is associated with significant short-term and long-term toxicities in pediatric patients. Anti-RET multikinase inhibitors are moderately effective and associated with significant toxicities in both adult and pediatric/adolescent patients. 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.

1.4 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 MTC, PTC, IM, CMN) that harbor RET alterations and/or depend on RET activity. This Phase 1/2 study of selpercatinib is required to understand the PK, safety, and MTD for selpercatinib in pediatric patients, and to permit the preliminary assessment of efficacy. Additional information is provided in the Selpercatinib a ≥ “–y)R •— ≥)4aR5:

1.5 SELPERCATINIB

Selpercatinib is a small molecule designed to block the adenosine triphosphate (ATP) binding site of the RET RTK; there is no evidence of covalent or irreversible binding. Selpercatinib

causes dose-dependent inhibition of tumor growth in multiple, biologically relevant RET-dependent tumor models in vitro and in vivo, including 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.

Additional information is provided in the Selpercatinib IB.

Figure 1-1 Effect of Selpercatinib on RET Fusions and Mutations In Cells

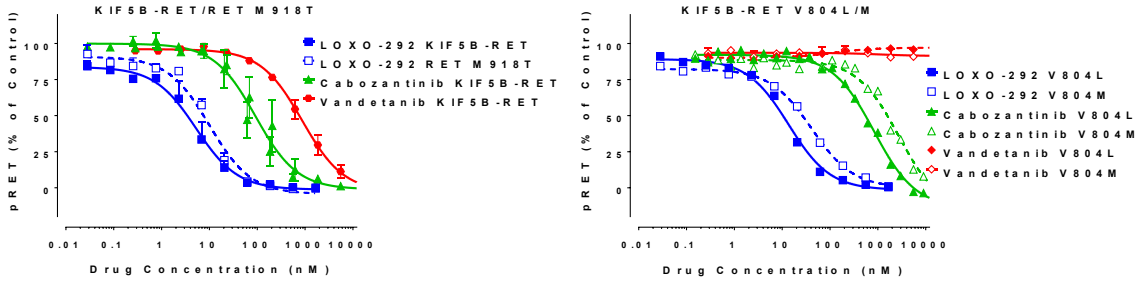

Figure 1-1. LOXO-292 = selpercatinib. Concentration-dependent inhibition of phosphorylated RET levels with selpercatinib was demonstrated in NIH 3T3 cells engineered to express four oncogenic RET proteins: KIF5B-RET, RET-M918T (left), KIF5B-RET-V804L and KIF5B-RET V804M (right). Cell lines were treated with a dose range of selpercatinib or cabozantinib and vandetanib as controls, and cellular phosphorylated RET levels were determined by in Cell Western assay. Data are shown as mean ± standard error of the mean.

Selpercatinib caused dose-dependent inhibition of tumor growth in multiple, biologically relevant RET-dependent tumor models, including: 1) allografts of NIH 3T3 cells engineered to express the KIF5B-RET fusion protein (-/+ V804M) found in human NSCLC; 2) xenografts of human cancer cell lines harboring endogenous *RET* gene alterations found in human lung cancer (CCDC6-RET fusion) and MTC (RET mutation encoding C634W); and 3) patient-derived xenografts (PDXs), including tumors harboring the challenging V804M anticipated acquired resistance mutation. In contrast, the MKIs cabozantinib and ponatinib were much less active against RET fusions with a V804M substitution (Figure 1-2).

Figure 1-2 Effect of Selpercatinib on RET Fusions and Mutations In Vivo

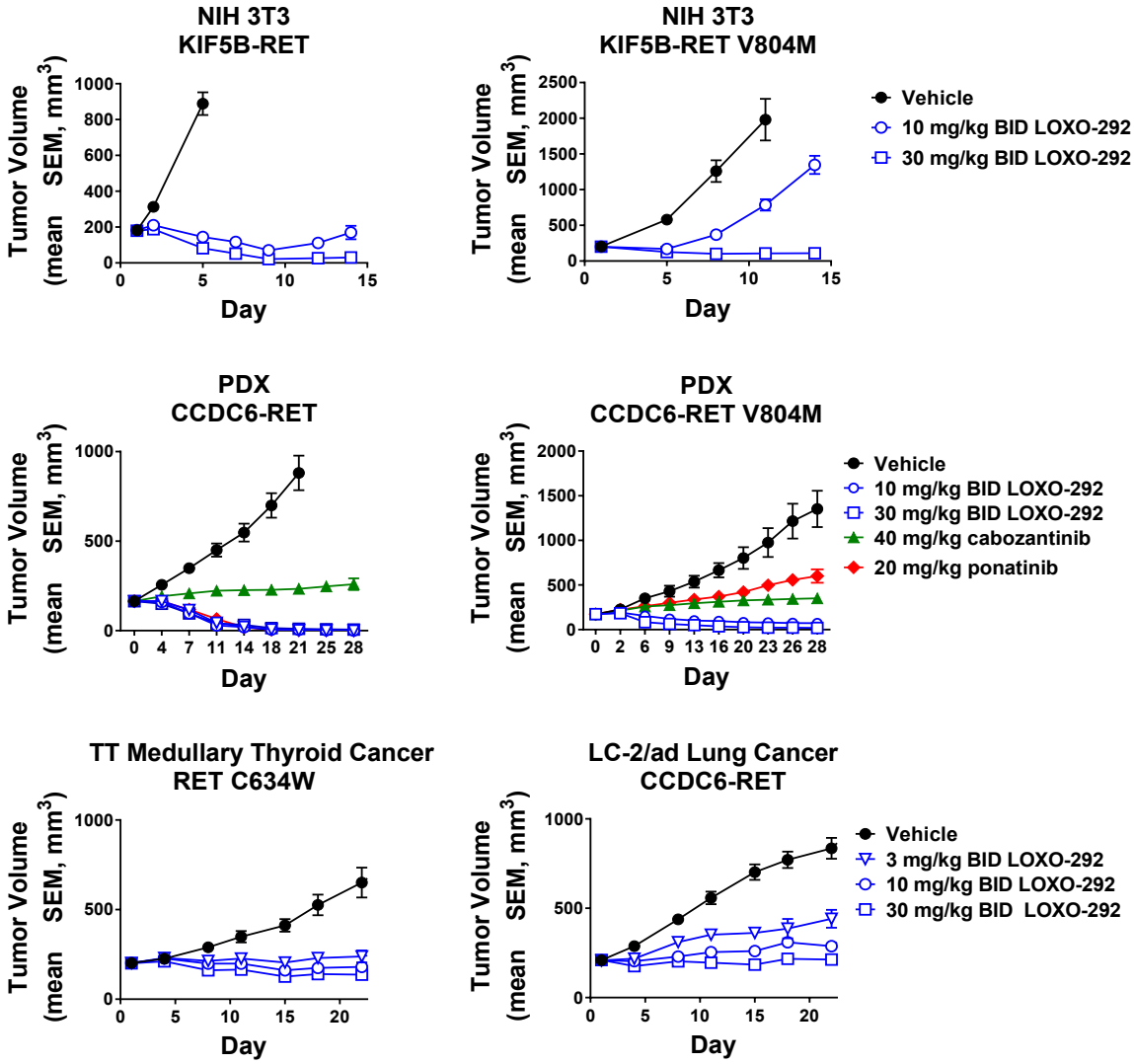

Figure 1-2. LOXO-292 = selpercatinib. Selpercatinib inhibits tumor growth in six RET-fusion/mutant allograft, xenograft or patient-derived xenograft (PDX) models. *Upper* Allograft: NIH 3T3-KIF5B-RET (left), NIH 3T3-KIF5B-RET V804M (right); *Middle* Xenograft: TT (RET C634W, MTC, left), LC-2/a (CCDC6-RET, NSCLC, right); *Lower* PDX: Parental (CCDC6-RET, colorectal cancer, left), Resistant (CCDC6-RET V804M, colorectal cancer, ponatinib-resistant, right, derived from Parental by continuous treatment of animals with ponatinib). Percent changes from baseline tumor volume in nude mice (n = 8 10/group) that were injected subcutaneously with tumor cells and treated with vehicle (control) or the indicated daily doses of selpercatinib are shown. For the PDCs, the effects of cabozantinib or ponatinib are also shown for comparison.

Finally, selpercatinib demonstrated potent anti-tumor activity against a RET-fusion patient-derived xenograft (PDX) implanted directly into the brain (Figure 1-3).

Figure 1-3 **Inhibition of Tumor Growth in a RET Fusion-Dependent Patient Derived Xenograft (PDX) Tumor Model Implanted into the Brain**

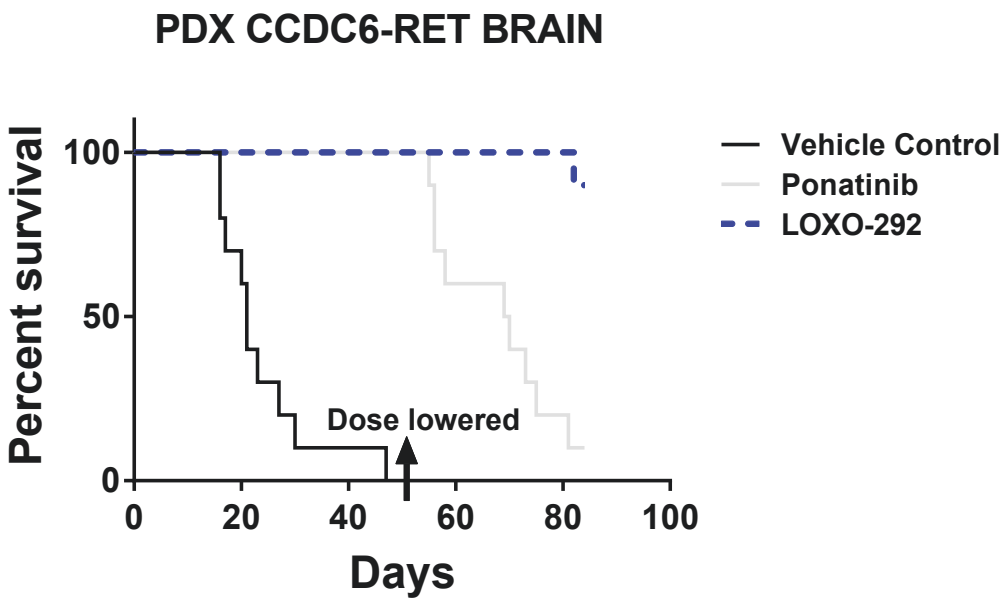

Figure 1-3. LOXO-292 = selpercatinib. Tumor suspensions of the CCDC6-RET fusion PDX were orthotopically injected into the brains of nude mice (Ncr:Nu/Nu). Seven days after implantation, mice were randomized (10 mice per group) and were dosed orally with selpercatinib (30 mg/kg twice daily [BID]), ponatinib (20 mg/kg once daily [QD], as a reference compound) or vehicle. Animals were evaluated daily for clinical status and were sacrificed if they exhibited central nervous system toxicity (e.g., unsteady gait, ataxia), discomfort, 20% or more body weight loss or if their clinical condition otherwise deteriorated. All vehicle-treated animals had to be sacrificed between Day 16 and Day 47 (median survival equal to 21 days). In contrast, both selpercatinib and ponatinib significantly prolonged survival up to 51 days after treatment initiation (median survival equal to 100% for each). To determine whether survival could be maintained with lower doses, the doses of each agent were lowered by the same fraction of the starting dose on Day 52 (e.g., selpercatinib from 30 mg/kg BID to 3 mg/kg BID, ponatinib from 20 mg/kg QD to 2 mg/kg QD). Following these dose adjustments, all but 1 ponatinib-treated animal had to be sacrificed by Day 84 (median survival equal to 19 additional days after the dose reduction). In contrast, 9/10 selpercatinib-treated animals survived to the end of the experiment on Day 84.

1.5.1 Pharmacokinetics

The pharmacokinetics of selpercatinib have been evaluated in both healthy volunteers and cancer patients, including, 4 pediatric single-patient protocol studies.

These data show that selpercatinib is well absorbed after oral administration to patients, with a median T_{max} of approximately 2 hours. AUC_{0-12} increases approximately 3-fold with repeated dosing. Doses of selpercatinib from 20 mg QD to 240 mg BID show approximately linear to slightly supra-proportional pharmacokinetics.

A dose of 160 mg BID in adult cancer patients resulted in a CCI [redacted] Accumulation from single to steady state dose is approximately 3.4-fold, CCI [redacted]

Pediatric dose has been selected as 92 mg/m^2, with a maximum dose of 160 mg BID, CCI

Selpercatinib has high permeability such that once it dissolves, selpercatinib can be absorbed readily from the gastrointestinal tract. Selpercatinib is a substrate for P-gp and BCRP in vitro, however these transporters do not appear to limit the oral absorption of selpercatinib, as its absolute oral bioavailability is CCI and its exposure was increased only minimally by co-administration of a P-gp inhibitor in a clinical study (increase of approximately CCI in selpercatinib AUC_{0-24} and C_{max}, respectively).

Selpercatinib has pH-dependent solubility, being more soluble in an acidic environment than a neutral one. This pH-dependent solubility led to a CCI in selpercatinib AUC when selpercatinib was given under fasted conditions to subjects treated with the acid-reducing agent omeprazole. The presence of food appears to mitigate the pH-dependent reduction in exposure.

In vitro, selpercatinib is metabolized essentially exclusively by CYP3A4 and therefore the effect a strong CYP3A4 inhibitor (itraconazole) and inducer (rifampin) on the PK of selpercatinib was evaluated. The strong CYP3A4 inhibitor itraconazole caused in an increase of approximately 130% and 30% in selpercatinib AUC and C_{max}, respectively, compared to selpercatinib alone and multiple doses of the strong CYP3A4 inducer rifampin resulted in a decrease of approximately 87% and 70% in selpercatinib AUC and C_{max}, respectively, compared to selpercatinib alone. These data confirmed that strong CYP3A4 inhibitors and inducers can affect the PK of selpercatinib. The effect of other strong and moderate inhibitors and moderate inducers of CYP3A4 was evaluated with a PBPK model, which predicted 148%, 118%, and 283% increases in AUC with the concomitant use of the moderate and strong CYP3A4 inhibitors fluconazole, diltiazem, and clarithromycin, and a 47% and 36% reduction in AUC with the concomitant use of moderate CYP3A4 inducers bosentan and modafinil, respectively.

In vitro selpercatinib showed no significant inhibition of CYP1A2, CYP2B6, CYP2C19, CYP2D6, and CYP3A4, but showed weak competitive inhibition of CYP2C8 and weak time-dependent inhibition of CYP3A4. Inhibition of CYP1A2, CYP2B6, CYP2C9, CYP2C19, or CYP2D6 at clinically relevant exposures of selpercatinib was considered unlikely based on in vitro data. Clinical drug interaction studies were conducted with a sensitive CYP2C8 probe (repaglinide) and a CYP3A4 probe (midazolam) to determine the potential for selpercatinib to inhibit these enzymes. Multiple-dose steady-state administration of 160 mg BID selpercatinib resulted in an increase of approximately 54% and 39% in midazolam AUC_{0-inf} and C_{max}, respectively, compared to midazolam alone and an increase of approximately 188% and 91% in repaglinide AUC_{0-inf} and C_{max}, respectively, compared to repaglinide alone.

A study in healthy volunteers has demonstrated that the 160 mg selpercatinib CCI is bioequivalent to the 2 × 80 mg capsule with no new safety findings.

1.5.2 Safety Pharmacology

As part of the development program for selpercatinib, three stand-alone safety pharmacology studies were conducted. Additionally, individual safety pharmacology endpoints (cardiovascular and CNS) were included in the study designs of the 28-day repeat-dose toxicity studies in the rat and minipig, and ECG's were evaluated in the 91-day study in minipigs.

In the GLP human ether á-go-go-related gene (hERG) assay, selpercatinib had an IC_{50} value of CCI, which is approximately 7-fold higher than the maximum unbound concentration at the clinical dose of 160 mg BID. In a stand-alone safety pharmacology study in minipigs, no cardiovascular effects were observed after single doses up to 12 mg/kg, the highest dose evaluated. In the 28-day minipig repeat-dose study, there were no ECG changes at doses up to 12 mg/kg, the highest dose evaluated. In the 91-day minipig repeat-dose study, females administered 5 mg/kg exhibited a non-adverse increase in QTc prolongation of approximately 12% and 7 %, relative to controls and pre-dose values, respectively. The dose of 5 mg/kg/day corresponded to a mean C_{max} approximately 0.2 times the human geometric mean maximum concentration at the clinical dose of 160 mg BID.

Respiratory function was assessed in a stand-alone safety pharmacology study in rats. Selpercatinib had no effects at single doses up to 45 mg/kg, the highest dose evaluated.

Neurobehavioral function was assessed in the 28-day repeat-dose study in rats with no definitive findings. Decreased locomotor activity, decreased mean forelimb grip strength, and lower values for fine movements or rearing were observed at the high dose only, and attributed to the animals' poor general condition.

1.5.3 Toxicology

Repeat-dose studies up to 91 days in duration were conducted in rats and minipigs to characterize toxicity in support of clinical development. Target organs of toxicity common to the rat and minipig were hematopoietic system, lymphoid tissues, tongue, pancreas, epiphyseal growth plate, and testes. In general, these toxicities in these organs were reversible; the exception was the testicular toxicity. Reversible toxicity was observed in the ovaries and gastrointestinal tract in minipigs only; at high doses, gastrointestinal toxicity caused morbidity in minipigs. Exposures in minipigs were generally lower than exposures determined in humans at the recommended dose. Target organs of toxicity observed only in rats were incisor teeth, liver, vagina, lungs, and Brunner's gland; also, multiple tissues were affected with mineralization associated with hyperphosphatemia. These toxicities only occurring in these organs in rats were reversible.

Selpercatinib is not mutagenic and is not genotoxic at therapeutic doses.

An embryo-fetal development study indicated that selpercatinib is a selective developmental toxicant, due to embryo lethality noted at all dose levels.

In a fertility study in male rats, there were no effects of selpercatinib on mating or fertility. However, at all doses, germ cell depletion and spermatid retention in the testes and increased cellular debris in the epididymis were observed dose-dependently. At the high dose only, these

effects were associated with reduced organ weights, reduced sperm motility, and an increase in the number of abnormal sperm.

In a fertility and early embryonic study in female rats, there were no effects of selpercatinib on mating or fertility. At the high dose only, a reduction in the number of estrous cycles with an increase in the pre-coital interval was observed, and there was an increase in the number of dead embryos, increased postimplantation loss, and a reduction in the number of live embryos.

Preliminary juvenile rat toxicology studies have been conducted with selpercatinib. These studies indicate that juvenile rats are less tolerant of selpercatinib than adult rats.

Additional details regarding the nonclinical toxicology studies are available in the IB.

1.5.4 Benefit/Risk

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 in the pediatric population, it is possible that unforeseen, unknown or unanticipated drug reactions and toxicities may occur. However, the clinical protocol is designed to mitigate risks to patients through a detailed plan for careful safety monitoring and management, systematic review of adverse events (AEs), serious adverse events (SAEs), PK, and active pharmacovigilance review to assess for safety signals or trends.

Pediatric patients with RET-fusion cancers (papillary thyroid, soft tissue sarcoma, others) and RET-mutated cancer represent populations with high unmet need. As discussed in Section 1.2 and Section 1.3 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 to be favorable.

1.5.5 Clinical Experience

As of 16 December 2019, a total of 702 patients have been treated with selpercatinib at doses ranging from 20 mg QD to 240 mg BID in Study LOXO-RET-17001 (LIBRETTO-001). Patients were initially enrolled in a dose escalation (3 × 3 design). During dose escalation, the dose of 160 mg BID was chosen as the dose for Phase 2, and subsequently, eligible and/or participating patients were dosed at 160 mg BID. Ninety-five percent (n = 667) of patients received at least one dose of the selpercatinib 60 mg, the majority of whom started treatment with a dose of 160 mg BID (n = 609 patients). All 702 patients were included in the safety analysis. *RET* alterations were documented in 686 (97.7%) of all patients.

At the time of this data cutoff, treatment is continuing in 548 of 702 (78.1%) patients, and treatment has been discontinued in 154 (21.9%) patients. The median age of patients was 59.0 years and ranged from 15 to 92 years. The majority of patients (n = 337, 48.0%) were 45 to

64 years of age; 239 (34.0%) patients were ≥ 65 years, 123 (17.5%) were 18 to 44 years, and 3 (0.4%) were under the age of 18 years.

As of 17 June 2019, Loxo Oncology has initiated [redacted] pediatric single patient protocols (SPPs), Special Access Scheme, or Temporary Authorization Use (ATU) cases to provide access to selpercatinib for patients with clinical need not meeting eligibility criteria for the ongoing clinical study.

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

1.5.6 Known and Anticipated Risks

As of a clinical data cut-off (May 8, 2022) for the LIBRETTO-001 FIH dose-finding study, 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.

1.5.7 Rationale for Selection of the Starting Dose

As outlined in Section 1.5.5, selpercatinib has been studied in an adult/adolescent Phase 1/2 trial (LOXO-RET-17001, LIBRETTO-001) where a recommended Phase 2 dose (RP2D) of 160 mg BID has been established with no MTD established.

As of August 24, 2018, preliminary steady-state PK data (CCI [redacted]) were available from 141 patients enrolled in the Phase 1 LOXO-RET-17001 study (Table 1-1). These data show that selpercatinib is absorbed after oral administration with a median T_{max} of approximately 2 hours (Figure 1-4). Although the plasma half-life could not be calculated with certainty because of the limited sampling interval (0-8 hours), based on an approximate CCI [redacted] Low concentrations of selpercatinib were recovered as unchanged drug in urine indicates that the kidney does not contribute to overall clearance. Steady-state PK profiles of selpercatinib in cancer patients are shown in Figure 1-4.

Of note, CCI [redacted]

Lee and colleagues reviewed cytotoxic chemotherapy Phase 1 trials in pediatric patients conducted between 1990 and 2004 (Lee JCO 2005). These authors reported that the MTD in children ranged between 80% and 160% compared to the adult MTD. Paoletti and colleagues (Paoletti et al. 2013) reviewed the dose-finding trials of 15 molecularly targeted agents in pediatric patients. The results of this meta-analysis revealed that the pediatric RP2D was 90%-130% of the adult RP2D in 70% of these agents. More importantly, the authors concluded that 63% of patients did not receive an optimal dose. A review of pediatric oncology studies revealed that when the pharmacokinetic/pharmacodynamic profile of the drug is not expected to be that different from adults, and when no cumulative toxicity is expected, it is reasonable to start by giving 80-100% of the body surface area (BSA)-adjusted adult dose to children, (Doussau et al. 2016).

In addition, as of 17 June 2019, [redacted] pediatric patients have been treated with selpercatinib through a compassionate use program.

LOXO-RET-18027 is an SPP which explored the use of selpercatinib in a 10-year old male with an expected RET-mutant MTC. The patient was dosed at 160 mg BID with the suspension formulation. CCI [redacted] The patient discontinued therapy C1D10 when further genomic profiling did not confirm a RET-alteration. The patient tolerated therapy with no Grade 3 or 4 events reported (Data on File, Loxo Oncology).

Data from the [redacted] patients with confirmed *RET* fusions are summarized in Table 1-2.

CCI

Characteristic	Patient LOXO-RET-18018	Patient LOXO-RET-18019	Patient LOXO-RET-18058	Patient LOXO-RET-19060	Patient LOXO-RET 19067
Country	CCI	CCI	CCI	CCI	CCI
Gender		Female	Female	Female	
Age at diagnosis		7 months	2 months	Birth	
Age at enrollment		13 months	21 months	21 months	
Diagnosis		Infantile myofibroma/hemangio-pericytoma	Congenital mesoblastic nephroma, infantile fibrosarcoma	Lipo-fibromatosis	
Primary tumor location		Paraspinal and retroperitoneal	Kidney, lung	Left foot	
Presence of metastases		n/a	Lung, brain	n/a	
***RET* alteration**		MYH10-RET	SPECC1L-RET	NCOA4-RET	
Dose		90 mg/m^2 (44 mg) BID	90 mg/m^2 (42 mg) BID	90 mg/m^2 (48 mg) BID	
AUC_{0-24} (ng*h/mL)		CCI	CCI	CCI	
Prior therapy		Chemotherapy, multikinase inhibitor	Chemotherapy, surgery	None	
Best RECIST response to selpercatinib		PR	PR	PR	
Duration of treatment (months) [a]		CCI	9CCI	CCI	

Abbreviations: AE = adverse event; AUC_{0-24} = area under the curve time 0 to 24 hours; BID = twice daily; NA = CCI

Selpercatinib PK data are available for CCI pediatric patients (Table 1-3): The estimated steady-state AUC_{0-24} in these patients was similar to that of adults treated with 160 mg BID selpercatinib (Figure 1-5). Note there is wide range of exposure in adults treated with 160 mg BID and the steady-state exposure of the pediatric patients is well within the range of exposures in adults given 160 mg BID.

Based on the known safety and PK profile in adults, the anticipation of similar toxicities, and prior experience in [redacted] pediatric patients, the starting dose for evaluation in the Phase 1 dose escalation is the BSA-adjusted adult RP2D dose (92 mg/m^2).

2 STUDY OBJECTIVES

Study objectives and endpoints are outlined below for Phase 1 (Section 2.1) and Phase 2 (Section 2.2).

2.1 Phase 1 Study Objectives

The objectives for the Phase 1 patient population (pediatric patients with an advanced cancer harboring an activating RET alteration) are as follows:

Primary

The primary objective is to determine the safety profile, including DLTs, of the oral RET inhibitor selpercatinib.

Secondary

- To characterize the PK properties of selpercatinib
- To identify the MTD and/or the RP2D and/or the appropriate dose of selpercatinib for further clinical investigation
- To describe the antitumor activity of selpercatinib

2.2 Phase 2 Study Objectives

The objectives for the Phase 2 patient population (pediatric patients with an advanced cancer harboring an activating RET alteration) are as follows:

Primary

To determine the objective response rate (ORR) as determined by an Independent Review Committee (IRC) and measured by the proportion of patients with best overall confirmed response of complete response (CR) or partial response (PR) by RECIST v1.1 or RANO criteria, as appropriate, following treatment with selpercatinib.

Secondary

- To determine the following:
  - ORR based on the treating Investigator's response assessment using RECIST v1.1 or RANO criteria, as appropriate to tumor type
  - DOR in patients with best overall response of CR or PR as determined by 1) an IRC and 2) the treating Investigator
  - Duration of PFS following initiation of selpercatinib by 1) an IRC and 2) the treating Investigator
  - OS following initiation of selpercatinib
  - CBR based on the proportion of patients with best overall response of CR, PR, or stable disease (SD) lasting 16 or more weeks following initiation of selpercatinib as determined by 1) an IRC and 2) the treating Investigator
- To assess the safety profile and tolerability of selpercatinib
- To characterize the PK properties of selpercatinib in pediatric patients
- To evaluate the concordance of prior molecular profiling that detected an activating RET alteration within the patient's tumor with diagnostic test(s) being evaluated by the Sponsor
- To characterize post-operative staging and surgical margin status in patients who have definitive surgery following treatment with selpercatinib
- To evaluate change from baseline in patient-reported pain at BOR visit as assessed by the Wong-Baker Faces Scale.
- To assess the acceptability and palatability of selpercatinib CCI [redacted] in patients under age 18

CCI [redacted]

Approved on 21 Feb 2025 GMT

3 INVESTIGATIONAL PLAN

3.1 Phase 1

3.1.1 Study Design

This is a multicenter, open-label, Phase 1/2 study in pediatric patients with advanced solid or primary CNS tumors harboring an activating RET alteration. Selpercatinib will be administered in oral liquid suspension or capsule(s)/CCI form BID, with the dose escalation according to evaluations of safety, efficacy, and PK with a BSA-based dose in all cohorts.

The starting dose level used in this study was based on a dose, 160 mg BID, which has been previously tested in adults and pediatrics. The dose frequency may be changed (e.g., QD dosing) based on the observed PK profile in pediatric patients.

The starting dose level is the current adult RP2D. Planned dose levels are listed in Table 3-1. BSA will be determined by the Mosteller (= $\sqrt{}$ height (cm) × weight (kg) / 3600 = BSA). A minimum of [redacted] patients will enroll in Dose Levels 1, and 2, also referred to as Dose Cohorts 1 and 2 respectively. The dose will be increased incrementally until a MTD or RP2D is identified. Increase or decrease in dose level if indicated, will follow the Table 3-1 dose levels listed, to the next appropriate dose.

Table 3-1 Planned Selpercatinib Dose Escalation Cohorts

Dose Level	Dose	Estimated Equivalent Adult Dose
-2	CCI	
-1		
1[a]		
2[a]		
3[a,b]		

Abbreviation: BID = twice daily.
a The Dose Levels listed, i.e., Dose Levels 1, 2, and 3, correspond to the Dose Cohorts 1, 2, and 3, respectively.
b Additional dose escalation may be considered based on the cumulative data (PK, safety, and efficacy) the actual dose determined by the SRC, not to exceed approximately 50% of the prior dose and taking into account capsule doses and capsule burden.

3.1.1.1 General Treatment Procedures

Patients will begin to receive the assigned selpercatinib dose on Day 1 (BID in accordance with the cohort assignment). Each cycle will consist of 28 days of continuous dosing; for patients who reach 2 years of study treatment, cycles may be extended to 84 days in length. The maximum dose (regardless of BSA calculation) will be no higher than the equivalent adult dose associated with the BSA-based dosing, i.e., patients in Dose Cohort 1 will receive a dose no higher than 160 mg BID, patients in Dose Cohort 2 will receive a dose no higher than 200 mg BID.

Individual patients will continue daily selpercatinib dosing until progressive disease (PD), unacceptable toxicity, or other reason for treatment discontinuation, as outlined in Section 5.3.4.4. Patients with PD may be allowed to continue selpercatinib if, in the opinion of

the Investigator, the patient is deriving clinical benefit from continuing study drug, and continuation of treatment is approved by the Sponsor.

Patients with locally advanced disease who achieve a radiologic confirmed PR (or better) by RECIST v1.1 may interrupt treatment beginning 1 year from confirmation of response. Such patients may undergo optional biopsy/optional positron emission tomography/computerized tomography (PET/CT) scan at the time of dose cessation for the purposes of more accurately quantifying the response to treatment. After interrupting treatment, such patients will be followed every 3 months with radiologic response assessment (computerized tomography [CT] or magnetic resonance imaging [MRI]) for up to 2 years, unless there is withdrawal of consent, initiation of new anti-cancer therapy, or the study ends. After 2 years, radiographic assessments will occur every 6 months. In addition, patients may undergo response assessment 1 month after interrupting selpercatinib at the discretion of the Investigator. Patients may re-start selpercatinib if there is evidence of PD after discontinuation of study drug (refer to Section 6).

Patients who undergo surgical resection for local control after treatment with selpercatinib (refer to Section 5.3.4.5 below for details of allowed surgeries) may continue to receive selpercatinib if a compelling clinical rationale is provided by the Investigator and approved by the Sponsor. Patients who undergo surgical treatment should have selpercatinib interrupted for 7 days prior to surgery and resumed 14 days after surgery. If the resection surgery results in negative margins (an R0 surgery) and study drug is interrupted, disease assessments, as described in Section 7.13, should be performed every 3 months following the last dose of study drug. These patients are permitted to restart study drug if they experience PD after discussion with the Sponsor's medical monitor.

All treated patients will undergo a safety follow-up visit at 28 days (+ 7 days) after the last dose of study treatment and long-term follow-up visits at 3-month intervals (± 1 month) and until the study is officially closed.

Patients who have an Ommaya Reservoir or are undergoing a routine diagnostic or staging lumbar puncture (LP) will have cerebral spinal fluid (CSF) in addition to a blood sample collected for PK assessment, CCI [redacted]

3.1.1.2 Dose Escalation Scheme and Assessment of Dose-Limiting Toxicity

The study employs a CCI [redacted] dose escalation CCI [redacted] patients will be enrolled in each dose cohort, also referred to as dose levels. Each patient will participate in only 1 dose cohort. The total number of patients to be enrolled in the dose escalation phase 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.

Escalation will proceed through the planned dose levels, or until the MTD is reached, or until the Sponsor, in agreement with the SRC, determines that a suitable dose has been achieved based on an overall assessment of safety, PK and toxicity. All patients in a given dose escalation cohort must have completed safety assessments through Cycle 1 Day 28 (C1D28) and must have

received a minimum of 75% of the planned total dose in Cycle 1 (unless due to toxicity) to be eligible for the assessment of a DLT. If a dose level is evaluated for MTD/RP2D and the Sponsor and Safety Review Committee (SRC) declare that dose level as the RP2D, and the enrolled patient population does not contain at least 2 patients aged 6 months to < 2 years, then the Phase 2 expansion can continue for patients greater than 2 years of age. Up to 2 patients aged 6 months to < 2 years will be over-enrolled in the dose level and evaluated to ensure this age group also meets the MTD/RP2D safety determination. Once this milestone has been achieved, patients aged 6 months to < 2 years may be eligible to enroll in Phase 2. Over-enrollment to these cohorts may occur in order to meet this requirement. An SRC may be convened for each cohort dose escalation but will only be required to convene prior to a cohort escalation if there is a DLT reported in a cohort.

If CCI patients within a cohort experience a DLT, then the dose escalation will cease. In order for the MTD/RP2D to be determined, the SRC will evaluate whether the previous lower dose level will be considered the MTD, whether an intermediate dose level should be evaluated, and/or whether additional patients need to be evaluated if the DLTs seen at this dose level are considered to be not serious or equivocal with regard to causal relationship to selpercatinib.

After completion of the 28-day DLT window in Cycle 1, patients may undergo intra-patient dose escalation to dose level(s) previously declared safe by the SRC if a compelling clinical rationale for dose escalation is provided by the Investigator and approved by the Sponsor.

3.1.1.3 Dose-Limiting Toxicity 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 5.0 (NCI CTCAE v5.0), occurring during the first 28 days of treatment, provided that the participant has received at least 75% of planned doses and the AE and not reasonably attributed to patient's underlying disease or other medical condition and deemed by the Investigator to be related to selpercatinib as assessed in accordance with CTCAE v5.0:

- Any Grade 3 or higher nonhematologic toxicity, with the exception of Grade 3 fatigue, nausea, tendon reflex decrease, or weight gain attributable to normal growth and development.
- Grade 3 vomiting or diarrhea will be considered DLT only if it persists > 48 hours despite standard of care treatment. Admission to the hospital of patients < 1 year of age with Grade 3 vomiting or diarrhea is recommended until these events resolve to Grade 1.
- Grade 4 vomiting or diarrhea will be considered DLT regardless of duration. Admission to the hospital of patients < 1 year of age with Grade 4 vomiting or diarrhea is recommended until these events resolve to Grade 1.
- Any toxicity, regardless of the NCI CTCAE v5.0 grade, resulting in discontinuation or dose reduction of treatment (with the exception of symptoms related to PD).
- Grade 4 thrombocytopenia or Grade 3 thrombocytopenia with Grade 1 or higher bleeding.

- Grade 4 anemia lasting > 8 days, despite supportive therapy, not explained by underlying condition (transfusions are allowed during Cycle 1), and persists beyond the initial transfusion.
- Grade 4 neutropenia, lasting > 8 days, despite supportive therapy (growth factor support during Cycle 1 not allowed for prophylaxis).
- Grade 3 uncomplicated febrile neutropenia *will not* be considered a DLT.

3.1.1.4 Number of Patients

A minimum of [redacted] patients are required to be enrolled in order to define the MTD/RP2D of selpercatinib. 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. Over-enrollment may occur in the dose escalation cohorts as previously described (Section 3.1.1.2).

If an eligible patient is identified after [redacted] patients have been enrolled to the current dose cohort and prior to clearance of the DLT window for these patients, the patient may be enrolled to a previous cohort that has been determined safe after discussion with the Sponsor's Medical Monitor. If this occurs during the DLT window for Dose Level 1, patients may be enrolled to Dose Level -1. Following clearance of the current dose level, the patient(s) enrolled to a previous level may have the dose escalated to a higher level that has been determined safe after discussion with the Sponsor's Medical Monitor.

Across Phase 1 and Phase 2 portion of the study, CCI [redacted]

In the Phase 2 portion of the study, additional patients may be enrolled to better characterize the safety and efficacy of the selpercatinib RP2D for further study. The Phase 2 portion will enroll approximately CCI [redacted] patients into Cohorts 1 and 2 (refer to Table 3-2 and Section 9.3); The total sample size for Phase 2 will not exceed CCI [redacted].

3.2 Phase 2 Dose Expansion Cohort

The Phase 2 portion of the study will open to enrollment when the MTD/ RP2D is confirmed and will enroll patients into one of 4 cohorts (refer to Table 3-2). To enroll in Cohorts 1 to 3, patients must have measurable disease. To be eligible for enrollment in Cohort 4, patients can have measurable or non-measurable disease. The expansion cohort will follow the same schedule of assessments as the dose escalation cohorts.

Table 3-2 Disease Criteria for Enrollment: Cohorts 1 to 4

Cohort	Disease Criteria
Cohort 1	RET fusion-positive solid tumor (excluding CNS primary) with measurable disease
Cohort 2	RET-mutant MTC with measurable disease
Cohort 3	RET fusion-positive primary CNS tumor with measurable disease
Cohort 4	Any patient with RET mutation/alteration not fitting Cohort 1 to 3 criteria (i.e., RET alterations via plasma cfDNA or non-CLIA certified test, measurable or non-measurable disease)

Abbreviations: cfDNA = circulating free DNA; CNS = central nervous system; MTC = medullary thyroid cancer.

3.3 General Treatment Procedures

Patients will receive selpercatinib on Day 1 in accordance with the Phase 1/2 cohort assignment. Each cycle will consist of 28 days of continuous dosing; for patients who reach 2 years of study treatment, cycles may be extended to 84 days in length.

Individual patients will continue daily selpercatinib dosing until PD, unacceptable toxicity, or other reason for treatment discontinuation, as outlined in Section 3.1.1.1. Patients who experience radiologic PD by RECIST v1.1 or RANO may be allowed to continue selpercatinib beyond PD if, in the opinion of the Investigator, the patient is deriving clinical benefit from continuing study drug, and continuation of treatment is approved by the Sponsor.

Patients with locally advanced disease with RECIST v1.1 confirmed response of CR/PR may interrupt treatment in a y“)y ≤) ≥≥)y y•—)l year from confirmation of response after discussion with the k)Medical Monitor (see Section 5.2.5 for additional information). These patients may undergo an optional tissue biopsy and/or additional imaging (e.g., PET/CT) at the time of consideration of treatment discontinuation. The purpose of these additional studies is to provide additional pathologic/radiographic information about disease status (e.g., presence or absence of tumor). Following treatment discontinuation, these patients will continue to be followed with radiologic assessment every 3 months for 2 years, and then every 6 months thereafter, using the same imaging modality(ies) as during treatment. An optional radiographic disease assessment may be performed 1 month after the interruption of selpercatinib at the ≤“ • ≥“) √)—≥)a ≥ “–y :)a√)y) y “≥)“) —“) y“)y ≤) ≥≥) ≥ “ ≤)“) ≥≤))–y ≥)≥ “<> •≥) of radiographic PD, the patient may re-start selpercatinib. At the time of selpercatinib re-initiation, the patient will start assessments per protocol as delineated for patients on active treatment. Patients who re-initiate selpercatinib treatment are permitted to have their selpercatinib treatment held again.

Patients who undergo surgical resection for local control may continue to receive selpercatinib after surgical recovery and discussion between the Investigator and the Sponsor. These patients should have selpercatinib held for 7 days prior to surgery and resumed 14 days after surgery. If the resection surgery results in negative margins and study drug is interrupted, disease assessments, as described in Section 7.13, should be performed every 3 months following the last dose of study drug. These patients are permitted to restart study drug if they experience PD after discussion with the k)medical monitor.

Patients under age 18 may be given an alternate formulation of selpercatinib for a defined duration for assessment of acceptability and, if appropriate, palatability.

All treated patients will undergo a safety follow-up visit at 28 days (+7 days) after the last dose of study treatment and long-term follow-up visits at 3-month intervals (± 1 month) and until the study is officially closed.

3.4 Investigational Sites

Approximately 25 institutions will be recruited to enroll patients.

4 SELECTION OF STUDY POPULATION

Potential patients and/or their parents must sign an Informed Consent Form (ICF) and Pediatric Assent Form, where applicable, before any study-specific Screening tests may be conducted.

4.1 Inclusion Criteria

Patients must meet all of the following criteria to be eligible for enrollment in the study:

1. Pediatric patients 6 months of age and 21 years of age at Cycle 1 Day 1 (C1D1) with a locally advanced or metastatic solid or primary CNS tumor that has relapsed, progressed or was nonresponsive to available therapies and for which no standard or available systemic curative therapy exists.
    a) Patients with locally advanced disease who would require, in the opinion of the Investigator, disfiguring surgery or limb amputation to achieve a complete surgical resection, are also eligible.
    b) In geographies where a selective RET-inhibitor is approved, patients may enroll without prior systemic treatment.
2. Evidence of an activating *RET* gene alteration in tumor and/or blood (e.g., gene rearrangement and/or mutation, excluding synonymous, frameshift, or nonsense mutations) as identified through molecular assays, as performed for clinical evaluation; refer to Appendix J for examples of *RET*-activating mutations.
    a) 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 in vitro diagnostic regulation compliance as applicable. In cases where such certification is not clearly demonstrated to determine eligibility, the Sponsor should be contacted to discuss laboratory test results.
    b) A positive germline test for a *RET* mutation is acceptable for patients with MTC.
    c) In addition to RET fusion-positive solid tumors and RET-mutant MTC, 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.
3. Patients with primary CNS tumors or cerebral metastasis:
    a) Must be neurologically stable based on stable neurologic exam for 7 days prior to enrollment.
    b) Must have not required increasing doses of steroids within the 7 days prior to enrollment to manage CNS symptoms.
4. Imaging study must be performed within 28 days of C1D1 while on stable dose steroid medication (if needed) for at least 7 days immediately before the imaging study.
5. Histologic verification of malignancy at original diagnosis or relapse, except in patients with intrinsic brain stem tumors, optic pathway gliomas, or patients with pineal tumors and elevations of CSF or serum tumor markers including alpha-fetoprotein or beta-human chorionic gonadotropin (HCG).
6. Must have measurable or non-measurable but evaluable disease.

7. Karnofsky (patients 16 years and older) or Lansky (patients younger than 16 years) performance score of at least 50.
8. Must have fully recovered from the acute toxic effects of all prior anti-cancer chemotherapy to CTCAE (v5.0) Grade 2.
    a) Myelosuppressive chemotherapy: Start of selpercatinib must be at least 21 days after the last dose of myelosuppressive chemotherapy (42 days if prior nitrosourea).
    b) Investigational agent or anticancer therapy other than chemotherapy: Not within 2 weeks prior to planned start of selpercatinib or 5 half-lives, whichever is shorter. Full recovery of clinically significant toxicities from that therapy must be evident. Prior MKIs with anti-RET activity are allowed. Refer to Appendix I for examples of MKIs with anti-RET activity. Patients who have previously received selpercatinib are not eligible.
    c) Radiation therapy (XRT): Start of selpercatinib must be at least 14 days after local palliative radiation (small port); at least 42 days must have elapsed before start of selpercatinib if other substantial bone marrow radiation, including prior radio-iodized metaiodobenzylguanidine (^{131}I-MIBG) therapy.
    d) Stem cell infusion (ASCT, Allogenic or CAR-T) without total body irradiation (TBI): No evidence of active graft versus host disease and at least 56 days must have elapsed before start of selpercatinib after transplant or stem cell infusion.
    e) Hematopoietic growth factors: Start of selpercatinib must be at least 14 days after the last dose of a long-acting growth factor (e.g., pegfilgrastim); or 7 days for short-acting growth factor.
9. An archival (FFPE or fresh frozen) or fresh tumor tissue sample must be available (refer to Section 7.5). If archival tumor tissue sample is not available, a fresh biopsy (at a primary or metastatic site) should be performed. If an archival or fresh sample cannot be obtained safely, the patient may still be eligible with documented Sponsor approval.
10. Adequate hematologic status, defined as:
    a) Qz „ ≥) ≥ —“;)•)4Qf S 5) 1.0 10^9/L not requiring growth factor support for at least 7 days prior to treatment.
    b) h„y ≥„≥)•) 75 10^9/L not requiring transfusion support for at least 7 days prior to treatment.
    c) Hb 8 mg/dL not requiring transfusion support or erythropoietin for at least 7 days prior to treatment.
11. Adequate hepatic / pancreatic function, defined as:
    a) Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) B:E) the upper limit of × y„)4mdf 5)) E) ULN with documented liver involvement (such as liver metastasis or a primary biliary tumor), *and*
    b) l y„)z“;“ z“) A:E) mdf)) C) ULN with documented liver involvement (patients “—)X“;z≥)T“ ≥y ≥)× y)z≥)≥ „„≥) “—)prior Sponsor approval).

12. Adequate renal function, defined as:

    a) U “× y ≥)–„ × ≥ „y)√„ y “) y ≥))C>)× d≪ “ <A:GC)× 2 based on local institutional practice for determination, or a maximum serum creatinine by age and gender as presented in Table 4-1.

Table 4-1 Serum Creatinine by Age and Gender

	Maximum Serum Creatinine (mg/dL)		Maximum Serum Creatinine (µmol/L)	
Age	**Male**	**Female**	**Male**	**Female**
6 months to < 1 year	0.5	0.5	44	44
1 to < 2 years	0.6	0.6	53	53
2 to < 6 years	0.8	0.8	71	71
6 to < 10 years	1	1	88	88
10 to < 13 years	1.2	1.2	106	106
13 to < 16 years	1.5	1.4	132	124
16 years	1.7	1.4	150	124

13. Ability to comply with outpatient treatment, laboratory monitoring, and required clinic visits for the duration of study participation.

14. Willingness of male and female patients with reproductive potential to utilize double effective birth control methods, defined as one used by the patient and another by his/her partner, for the duration of treatment and for 1 month following study completion.

    For male patients with a non-pregnant female partner of child-bearing potential, and woman of child-bearing potential, one of the following highly effective birth control methods (with a failure rate of less than 1% per year when used consistently and correctly) are recommended:

    a) Combined estrogen and progestogen containing hormonal contraception associated with inhibition of ovulation given orally, intravaginally, or transdermally
    b) Progestin-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: considered a highly effective method only if defined as refraining from heterosexual intercourse during an entire period of risk associated with the study treatment. The reliability of sexual abstinence will be evaluated in relation to the duration of the study and to the usual lifestyle of the patient.

    Birth control methods ***unacceptable*** for this clinical trial are:

    a) Periodic abstinence (calendar, sympto-thermal, or post-ovulation methods)
    b) Withdrawal (coitus interruptus)
    c) Spermicide only

d) Lactational amenorrhea method

15. Ability to swallow capsules, liquid suspension, or gastric access via a naso- or gastric tube.
16. The patient and, when applicable, the parent/guardian of child or adolescent patient has the ability to understand, agree to, and sign the study Informed Consent Form (ICF) and applicable Pediatric Assent Form before initiation of any protocol-related procedures; patient has the ability to give assent, as applicable, at the time of parental/guardian consent.
17. [removed]

4.2 Exclusion Criteria

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

1. Major surgery within 2 weeks prior to C1D1.
2. Clinically significant active cardiovascular disease or history of myocardial infarction within 6 months prior to C1D1; ongoing cardiomyopathy; or current prolonged QT interval • ≥• ≥≤)√)—≥y) y ≥)4i 1 • 5)" ≥ y,,)N)DD>)× ",," ≥• ≤)√) y "≥))AE) ≥y) ,≤)y ≤)N) 470 milliseconds √) y "≥)N)AE) ≥y) ,≤:)V) y "≥))AE) ≥y) ,≤8)Ry ≥)V × ,y) will be utilized to determine QTc. For patients > 15 years old, either method, Fridericia or Ry ≥)V × ,y)× y)z≥)y ,,"≥≤:
3. Active uncontrolled systemic bacterial, viral, or fungal infection, which in the opinion of the Investigator makes the risk: benefit ratio for the patient to participate in the trial unfavorable. Screening for chronic conditions is not required.
4. Clinically significant active malabsorption syndrome or other condition likely to affect gastrointestinal absorption of the study drug.
5. Pregnancy or lactation.
6. Uncontrolled hypotension or hy ≥ ≥ "))X y≤≥)C)S1 SQU)4 5.0).
7. Uncontrolled symptomatic hyperthyroidism or hypothyroidism (i.e., the patient required a modification to current thyroid medication in the 7 days before start of selpercatinib).
8. Uncontrolled symptomatic hypercalcemia or hypocalcemia.
9. [Removed]
10. Known hypersensitivity to any of the components of the investigational agent, selpercatinib or Ora-Sweet® SF and OraPlus®, for patients who will receive selpercatinib suspension.
11. [Removed]
12. [Removed]

4.3 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/prior to eligibility for review prior to patient enrollment. As part of pre-screening, it is advised to provide this upon patient identification for the study.

A representative from the investigational site will contact the Sponsor or designee when a potential study candidate is identified, a patient 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 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.

5 TREATMENT

5.1 Investigational Product

Selpercatinib will be provided as a liquid suspension with a concentration of CCI, capsules in strengths of 40 mg and 80 mg, or CCI in strength of 40 mg and 160 mg.

The capsules and CCI will be provided to the sites for distribution to the patient for outpatient administration. The site personnel will dispense investigational product to the patient in an amount necessary to allow for outpatient administration at the assigned dose level.

Selpercatinib liquid suspension is provided as selpercatinib powder, which consists of the drug substance filled into a glass bottle or other suitable container with a child-resistant closure. It is compounded in the pharmacy CCI CCI CCI The prepared selpercatinib liquid suspension is to be stored at CCI

Intervention Name[a]	Selpercatinib		
Dosage Level(s)	Liquid suspension CCI mg/mL	40 mg and 80 mg capsules	40 mg and 160 mg CCI
Authorized as defined by EU Clinical Trial Regulation	Not authorized in EU	Authorized and not used according to EU authorization	Not authorized in EU

[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 are provided in the Pharmacy Manual and the Selpercatinib IB.

Packaging and labeling

Study drug 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.

5.2 Selpercatinib Administration

5.2.1 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.

Liquid suspension or CCI will be administered orally, or enterally via a nasogastric or gastrostomy feeding tube with a dosing syringe. For patients taking proton pump inhibitors

(PPIs), selpercatinib should be taken with a meal. Otherwise, there is no food restriction relative to the dosing time of selpercatinib (capsules, CCI or liquid suspension).

If the patient spits out all of the liquid suspension immediately, they should be given another dose. If, after two attempts, the patient does not swallow the dose, it will be considered a "missed" dose. If this occurs during the time period the drug diary is required, record the missed dose in the diary as "missed" and note next to the entry that the patient "spit out the dose."

If the patient swallows the liquid suspension or CCI and vomits after ingesting it, another dose should not be given at that time. If the patient vomits the capsule(s)/CCI and they are still recognizable, then the patient can be re-dosed. If the patient vomits capsule(s)/CCI contents and the capsule/CCI is not recognizable, the patient or parent should be instructed to call the Study doctor or nurse to discuss if they should take any additional capsules/CCI .

Late doses (i.e., 4 or more hours after the scheduled time) should be noted in the diary (if diary required during that cycle). Doses that are late by > 6 hours should be skipped and recorded in the dosing diary (if diary required during that cycle) as missed. The patient, or the patient's parent or legal guardian, will keep a daily diary to record dosing compliance during Cycles 1-3 and as directed. Compliance will also be assessed at each clinic visit by means of a capsule/CCI count in the returned bottle, or liquid level verification in the suspension bottle(s).

Since selpercatinib absorption from the GI tract may be impacted by stomach acidity, agents which may alter stomach pH require additional considerations for administration. Instructions for taking PPIs, histamine-2 (H2) blocking agents and antacids, if clinically indicated, are provided in Section 5.3.4.1 and 5.3.4.2. Refer to Appendix G for examples of PPIs and for additional information. Patients taking these agents are encouraged to record the time of each dose in relationship to each dose of selpercatinib in the dosing diary (when diary is in use; inaccurate recording will not be considered a protocol violation) (refer to Section 5.2.1). Any questions regarding dose rounding should be directed to the Sponsor.

Patients will begin BID dosing on C1D1 according to the assigned cohort. Serial blood samples for PK monitoring will be collected as outlined in Section 7.12 and Appendix B. The blood volume collected should not exceed institutional guidelines.

Selpercatinib dose rounding rules are provided in Appendix H. Any questions regarding dose rounding should be directed to the Sponsor and Medpace medical monitors.

All patients will start treatment with capsule or liquid suspension, as appropriate, and will continue that formulation at least through the end of Cycle 3. After Cycle 3, CCI or CCI as an alternate formulation of selpercatinib may be given to patients less than 18 years of age for a defined duration (e.g., one 28 day cycle) for assessment of the acceptability and palatability, as individually directed by the Sponsor. Dosing diary will also be completed during the alternate formulation period.

5.2.2 Cycle 1

Patients will begin BID dosing on C1D1 according to the assigned cohort. Serial blood samples for PK monitoring will be collected and the patient will be monitored for safety as outlined in Section 7. The blood volume collected should not exceed institutional guidelines. 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 to 28.

5.2.3 Cycles 2 and Higher

In accordance with the assigned dose level, each patient will receive selpercatinib in continuous 28-day or 84-day cycles until treatment discontinuation. Serial blood samples for PK monitoring will be collected and the patient will be monitored for safety as outlined in Section 7.12 and Appendix B.

5.2.4 Dose Modifications

Table 5-1 outlines toxicities that may require dose modification. Patients who experience a clinically significant (> Grade 2 [i.e., Grade 3 or 4] or a 1 grade change from baseline when baseline is abnormal at Grade 2 or higher) hematologic or non-hematologic AE should have selpercatinib dosing interrupted for no longer than 28 days to evaluate the AE and to allow for recovery (to Grade 1 or baseline level). Upon recovery of the AE unrelated to the dose level of selpercatinib and/or symptoms associated with the AE, dosing may be restarted at the same dose.

If the AE is considered related to the dose level of selpercatinib, but has returned to baseline level within 28 days, then the dose may be reduced to the next lower dose level. The number of times that a dose may be reduced is dependent upon the starting dose that the patient received. Patients who have been dose reduced for treatment-related AEs may be dose re-escalated after resolution of the AE and demonstration that they have tolerated study drug at the reduced dose for at least 1 full treatment cycle, after discussion with and approval from the sponsor. Additional guidance is found in the IB. Patients who miss 7 or more days of dosing in Cycle 1 for reasons other than study drug-related toxicity are not evaluable for the DLT window and will be replaced. If a patient is tolerating selpercatinib without evidence of PD, after Cycle 1, the patient may have the dose increased to a dose that has already been established as tolerable by the SRC8y ≤) “–)–≥)y– ≥≥× ≥) √)–≥)k)Medical Monitor.

If a dose interruption includes Day 1 of the next cycle, the next cycle will start with resumption of study drug. If a dose interruption does not include Day 1 of the next cycle, the cycle should remain 28 days in length. All dose interruptions and dose modifications and the reasons for those changes will be recorded in the electronic Case Report Form (eCRF).

The National Cancer Institute (NCI)-developed CTCAE should be used when evaluating toxicities. According to the NCI-CTCAE (version 5), adverse reactions are reported by grade (level of severity) on the scale of Grades 1 to 5. Generally, the descriptions for adverse reactions by grade level (scale of Grades 1 to 5) follow the guidelines outlined below in Section 8.1, Table 8-1.

Table 5-1 Toxicities Requiring Dose Modification

Toxicity	Dose Modification
Interstitial Lung Disease/Pneumonitis	For Grade 2: Withhold selpercatinib until resolution. Resume at next lower dose. Discontinue selpercatinib for recurrent interstitial lung disease /pneumonitis. For Grade 3 or 4, discontinue selpercatinib.
Increased ALT or AST, Grade 3 or 4	Suspend dose until toxicity resolves to baseline or Grade 1. Resume selpercatinib at the second dose reduction twice daily. If after at least 2 weeks selpercatinib is tolerated without recurrent increased ALT or AST, selpercatinib dosing can be increased to the first dose reduction. If selpercatinib is tolerated at the first dose reduction for at least 4 weeks without increased ALT or AST, dosing can be increased to dose taken prior to the onset of Grade 3 or 4 increased ALT or AST. Permanently discontinue selpercatinib if Grade 3 or 4 increased ALT or AST recur despite dose modifications.
Hypersensitivity	Suspend dose until toxicity resolves and start steroid treatment. Resume selpercatinib at 40 mg twice daily while continuing steroid treatment. If after at least 7 days selpercatinib is tolerated without recurrent hypersensitivity, incrementally increase the selpercatinib dose to 80 mg twice daily for 7 days, followed by 120 mg twice daily for 7 days. For patients with an originally prescribed dose of 160 mg twice daily, if selpercatinib is tolerated at the 120 mg twice daily dose for 7 days, subsequently increase the dose to 160 mg twice daily. Prior to dose increase, always ensure that selpercatinib is tolerated for at least 7 days. Start steroid tapering after selpercatinib has been tolerated for at least 7 days at the final dose. Discontinue selpercatinib for recurrent clinically significant hypersensitivity.
QT Interval Prolongation	Suspend dose for QTcF intervals >500 ms until the QTcF returns to <470 ms. Resume selpercatinib treatment at the next lower dose level. Permanently discontinue selpercatinib if QT prolongation remains uncontrolled after 2 dose reductions or if the patient has signs or symptoms of serious arrhythmia.
Hypertension, Grade 3 or 4	Ry ≥„“ ≥)z„ ≤) ≥ ≥) y„ ≥) — „≤)z≥) AD><I >)× × Y–)(or <95th percentile for age for children) before starting selpercatinib. Temporarily suspend selpercatinib for severe hypertension until controlled with medical management. Resume dosing at the next lower dose if clinically indicated.
Other clinically significant AE	For Grade 3 or Grade 4 AE, or 1 grade change from baseline when baseline is abnormal at Grade 2 or higher: Hold dosing for up to 28 days to allow recovery (to Grade 1 or baseline) If unrelated to study drug, restart at same dose If related to study drug, reduce to lower dose (refer to Table 5-2)

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase.

Additional information regarding the management of AEs (e.g., chylothorax, hemorrhage, etc.) can be found in the IB.

Table 5-2 Dose Level Reductions for Selpercatinib

Dose Level [a]	Dose	Estimated Equivalent Adult Dose	Dose of Selpercatinib
Starting Dose (1)	CCI	160 mg BID	Originally assigned dose level
First Dose Reduction (-1)		120 mg BID	Reduce dose by at least one dose level
Second Dose Reduction (-2) [b]		80 mg BID	Reduce dose by at least one additional dose level

[a] The Dose Levels listed, i.e., Dose Levels 1, -1, and -2, correspond to the Starting Dose, First Dose Reduction, and Second Dose Reduction, respectively.
[b] If a third dose reduction is required the Investigator must contact the Sponsor to discuss the best dosing strategy for the patient depending on the reason for dose reduction and clinical benefit.

5.2.5 Drug Treatment Holiday

If requested by Investigators, patients with durable (i.e., at least 24 months) radiographic and clinical disease control may be approved for a drug treatment holiday and remain in observation on trial. The duration of the holiday will be determined by Investigator and Sponsor before initiation of the holiday. Patients will continue to follow the Schedule of Assessments as per the long-term follow-up schedule with additional evaluations as appropriate for the standard of care/Investigator discretion. If patients experience disease progression during drug treatment holiday, they may resume selpercatinib starting with the next subsequent cycle number and assessments from the date of the initiation of the drug treatment holiday.

5.3 Prior and Concomitant Medications

5.3.1 General

All medications that were used from 14 days prior to first dose through the Safety Follow-up visit will be recorded in the eCRF. These are to include prescription and nonprescription medications, transfusions, vitamins and nutritional supplements, and other remedies. Refer to Section 5.3.3 for information regarding prior medications that are excluded via eligibility criteria.

5.3.2 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 or thrombocytopenia in accordance with American Society for Clinical Oncology (ASCO) and/or European Society for Medical Oncology guidelines, transfusions, anti-emetics and anti-diarrheals, and glucocorticoids (up to 10 mg dexamethasone or 50 mg of prednisone or equivalent), including short courses to treat asthma, chronic obstructive pulmonary disease (COPD), or other systemic, chronic diseases that are normally treated with short courses of

glucocorticoids. As selpercatinib is a substrate of CYP3A4, patients should avoid inhibitors or inducers of CYP3A4 if possible y)–≥)• ,,≤)y,,≥)–≥)≤ –)hc : Continuation of standard of care or supportive care medications that the patient has been on for the previous 28 days are allowed.

Higher doses of glucocorticoids (e.g., dexamethasone) may be administered to primary brain tumor patients to reduce peritumoral edema and improve neurological deficits. However, patients should remain on a stable dose (i.e., same daily dose) in the 7 days prior to, and on the day of, all protocol-defined MRI scans (including the Screening MRI). Anti-seizure medications should be used as indicated.

Enzyme-inducing anti-epileptic drugs (EIAEDs) and dexamethasone for CNS tumors or metastases, on a stable dose, are allowed. If, for unavoidable clinical reasons (i.e., severe allergies, toxicities), a patient)y “-epileptic drug is changed, the following guidelines must be followed:

Patients who were previously on a non-EIAED and need to change anticonvulsants should be started on another non-EIAED if at all possible. No delays in treatment would be required.

Patients who were previously on a non-EIAED and were inadvertently and temporarily changed to an EIAED should immediately be started on another non-EIAED. The patient may continue the current treatment dose selpercatinib while a non-EIAED is re-started.

Patients who were previously on a non-EIAED and need to permanently change anticonvulsants, but who cannot change to another non-EIAED, must be discussed with the Sponsor.

Patients who were previously on an EIAED and need to permanently change or stop anticonvulsants, but who cannot change to another EIAED must be discussed with the Sponsor.

5.3.3 Prohibited Concomitant Medications

5.3.3.1 Chemotherapeutic Agents or Hematopoietic Growth Factors

In addition, except as indicated in Section 5.3.2, patients are not allowed to receive other chemotherapeutic agents, hematopoietic growth factors for prophylaxis in Cycle 1, anti-cancer monoclonal antibodies, radiation therapy (other than palliative radiation, refer to Section 5.3.4.4), drugs with immunosuppressant properties administered systemically (topical/local applications, e.g. for atopic dermatitis, are allowed), or any other investigational agents besides selpercatinib. No new, alternative anticancer therapy is allowed prior to documentation of PD in accordance with protocol-specified disease response criteria.

5.3.4 Concurrent Medications, Therapy, or Surgery

5.3.4.1 H2 Blockers

When concurrent use of an H2 blocking agent is necessary, e.g., ranitidine, famotidine, or cimetidine, it must be administered only between 2 and 3 hours after the dose of selpercatinib. If not taken during this time, the dose of H2 blocking agents should not be taken again until 2 to 3 hours after the next dose of selpercatinib.

5.3.4.2 PPIs

When concurrent use of a PPI cannot be avoided, e.g., omeprazole, it must be administered with food. When selpercatinib is given in the fasted state with gastric pH modification by omeprazole, the exposure (C_{max} and AUC) is reduced. The presence of food mitigates the omeprazole-induced reduction in exposure; when selpercatinib is given with a low-fat or high-fat meal to subjects treated with omeprazole, there was no significant change in selpercatinib exposure.

5.3.4.3 Antacids

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

5.3.4.4 Palliative Radiotherapy

Palliative radiotherapy to specific sites of disease is permitted if considered medically necessary by the treating physician. Selpercatinib should be held for 3 days before and 3 days after treatment. Selpercatinib may be held for a shorter time if a compelling clinical rationale (e.g., risk of disease flare) is provided by the Investigator and approved by the Sponsor. In general, target lesions being used to measure response should not be irradiated without discussion with the Sponsor Monitor, and may be reason for the patient to be removed from study for PD. Irradiated lesions will be considered not evaluable for response, but still can be used to assess PD. The intensities, number, and dates of doses received for allowed palliative radiotherapy should be recorded on the appropriate eCRF.

5.3.4.5 Elective Surgery or Surgical Resection

Although selpercatinib is not expected to significantly affect wound healing, any unusual findings should be recorded as potential AEs. In the event of a major surgery requiring general anesthesia (elective or not) during study participation, it is recommended that selpercatinib be held 7 days before surgery and resumed 14 days after surgery, or later if wound healing is delayed.

For patients who receive selpercatinib prior to attempted surgical resection, selpercatinib should be continued in a tumor deemed responsive to selpercatinib, until tumor resectability is possible. Patients may undergo surgical resection when, in the opinion of the treating Investigator, the tumor is resectable without mutilating surgery or limb amputation. If the resection surgery results in negative margins and study drug is held, disease assessments, as described in Section 7.13,

should be performed every 3 months following the last dose of study drug. These patients are permitted to restart study drug if they experience PD after discussion with the k)Medical Monitor. Long-term follow-up will occur as outlined in Section 7.19.

Patients who receive selpercatinib and go on to an attempted surgical resection will be re-staged just prior to surgery. Staging will be defined per tumor appropriate radiographic assessment and aligned with the radiographic method set at Screening. Patients who undergo surgical local control may -resume selpercatinib after recovery and discussion between the Investigator and the Sponsor. If the resection results in negative margins or otherwise considered curative and study drug is held, clinical and disease assessments, as described in Section 7.13, should be performed every 3 months following the last dose of study drug. These patients are permitted to restart study drug if they experience PD after discussion with the k)Medical Monitor.

5.3.4.6 Inhibitors or Inducers of CYP3A4

As selpercatinib is a substrate of CYP3A4, patients should avoid strong or moderate inhibitors or inducers of CYP3A4 as they could alte) –≥)≤ –)hc . This includes herbal products such as St b —) , grapefruit, and grapefruit juice, which may decrease the levels of selpercatinib. Refer to Appendix D for lists of example inhibitors and inducers of CYP3A4. In discussion with the sponsor, dose reduction may be allowed for patients who cannot avoid concurrent strong CYP3A4 inhibitors.

5.4 Duration of Treatment

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 6.1 Removal of Patients from Therapy or Assessment), or if the patient has chosen to withdraw from the study:)m)• × × ≥ •‘y,,)y y‘;yz“;“)“)≥y•—) y ‘≥) ≥ ≥• “ ≥)• ry, there may be additional options for the patient to continue to receive selpercatinib once the regulatory requirements are satisfied. These may include but are not limited to a rollover trial, patient assistance (should the patient qualify), or commercial selpercatinib. 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.

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

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

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

The y ‘≥ continued access to study intervention will end when a criterion for discontinuation is met (Section 6). Continued access follow-up will begin the day after the participant and the

investigator agree to discontinue study intervention and lasts approximately 30 days following the last dose of study drug. Follow-up procedures will be performed as shown in the Continued Access SoA (Appendix KAppendix KAppendix KAppendix K).

Participants who are in safety follow-up when the continued access period begins will continue in short−term follow-up until the 28-day safety follow-up visit is completed.

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.

6 DISCONTINUATION / WITHDRAWAL CRITERIA

6.1 Removal of Patients from Therapy or Assessment

Patients will be advised that they are free to withdraw from the study at any time. Over the course of the study, the Investigator and/or the Sponsor may withdraw a patient from treatment for any of the reasons listed below:

Disease progression (PD), except:

if in the opinion of the Investigator, the patient is deriving clinical benefit from continuing study drug, and continuation of treatment is approved by the Sponsor, OR in the occurrence of PD during a planned drug treatment holiday and resumption of study treatment is considered in the best interest of the patient by the Investigator.

Adverse Events

Intercurrent illness compromising ability to fulfil protocol requirements

Requirement for alternative treatment in the opinion of the Investigator

Significant noncompliance to protocol

Pregnancy

Withdrawal of consent or assent by the patient

Lost to follow-up

Death

Complete surgical resection (removal from therapy, but not further assessment)

Patients who undergo surgical resection for local control may continue to receive selpercatinib after surgical recovery and discussion between the Investigator and the Sponsor. These patients should have selpercatinib held for 7 days prior to surgery and resumed 14 days after surgery. If the resection surgery results in negative margins and study drug is held, disease assessments, as described in Section 7.13, should be performed every 3 months following the last dose of study drug. These patients are permitted to restart study drug if they experience PD after discussion with the k)medical monitor.

When a patient stops treatment, all safety data normally required at the end of treatment (EOT) visit will be obtained if possible, as outlined in Section 7.17.

6.2 Reasons for End of Study

Reasons for end of study could be:

Withdrawal of consent or assent by the patient

Lost to follow-up

Death

Study terminated by Sponsor

Completed the last visit where the patient completed the SFU visit, or completes any applicable continued access follow-up

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 in which character, severity or frequency is new in comparison to the existing risk profile. Q) y••≥ yz,≥) "•") ",,)z≥)• "≤≥)y) ≥y × ≥)≥× ≥ –≥)y≤ ≥ ≥)≥ ≥) –y)")) Grade 3 or intolerable Grade 2 and considered related to study drug and that continues despite protocol allowed dose reduction. In addition, any data deriving from other clinical trials or toxicological studies which negatively influence the risk/benefit assessment may cause discontinuation or termination of the study.

7 STUDY PROCEDURES AND ASSESSMENTS

Descriptions of assessments are provided in Sections 7.1 through 7.19, below. Specific timing requirements for study procedures and assessments are provided in Appendix A, Table 11-1, and are described in more detail in the following subsections.

Routine laboratories, for example serum chemistries, hematology, and urinalysis, will be performed locally. Special assessments such as PK and correlative studies will be performed centrally or as individually indicated. For each MTC patient, tests for calcitonin and CEA should be performed in the same laboratory to minimize intra-patient, lab-to-lab variability in their measurement. Additional information on the handling and processing of these special samples is provided in the separate Laboratory Manual.

7.1 Informed Consent / Pediatric Assent

Patients must be able to provide written informed consent (or pediatric assent, when applicable) and meet eligibility criteria prior to enrollment. Separate ICFs will be required for patients enrolling in Phase 1 and in Phase 2. Additional details are provided in Section 10.1.3.

7.2 Screening

The Screening procedures must be conducted 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 ≥≥) z y“ ≍≍)y) y) √) –≥) y ‘≥) y ≤y ≤)•y ≥) “)) ‘≤“ –)“ √ ×≍ consent for this study, with documented Sponsor approval. 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 11-1) 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.

7.3 Enrollment

Enrollment procedures will be conducted in accordance with the Schedule of Assessments (Table 11-1). Patients who meet eligibility criteria outlined in Section 4 will be enrolled in this study. A patient may be enrolled in either Phase 1 or Phase 2 of the study, but not both. In both Phase 1 and 2, the Investigator may repeat qualifying laboratory tests and vital signs/ ECGs prior to enrollment if a non-qualifying finding is considered an error, and/or if an acute finding is likely to meet eligibility criteria on repeat testing.

7.4 Medical History and Malignancy History

All conditions ongoing and relevant past surgical and medical history should be collected in accordance with the Schedule of Assessments (Table 11-1). Medical, surgical, and malignancy history, including histologic confirmation of solid tumor, primary and metastatic diagnosis dates, prior treatments for the malignancy, etc. should be recorded on the appropriate eCRF. Demographics including age, gender, race, and ethnicity will be recorded.

7.5 Tissue Biopsy

Tissue biopsies should be collected in accordance with the Schedule of Assessments (Table 11-1). Availability of tissue biopsy is required following the most recent progression. If tissue meeting this criterion is not available, a tissue sample obtained prior to most recent progression is acceptable. If neither of these samples are available for submission, then a fresh tumor biopsy is requested if it can be safely obtained. If no tissue is available, the patient may still be eligible for enrollment following conversation with the Sponsor. Tissue biopsy collected at the EOT visit is optional. Additional biopsies may be requested on a case-by-case basis in patients re-starting study drug following a drug holiday and disease recurrence. All specimens will be deidentified and stored at a secure facility designated by the sponsor for up to 15 years from the date of receipt.

7.6 Physical Examination

Physical examinations will be conducted in accordance with the Schedule of Assessments (Table 11-1) and will include review of systems (breast/chest, extremities, genitourinary, head/ears/eyes/nose/throat, lymph nodes, musculoskeletal, pulmonary, and skin), thorough neurologic assessment, body weight, and height during Screening. Symptom-directed physical examination and neurological examinations, including measurement of weight and height, may be performed at other time points after Screening in accordance with the Schedule of Assessments (Table 11-1).

7.6.1 Karnofsky or Lansky Performance Status Scales

Karnofsky or Lansky Performance Status Scales will be conducted in accordance with the Schedule of Assessments (Table 11-1). The Karnofsky score should be assessed for patients 16 years old or older, or the Lansky score should be assessed for patients younger than 16 years (refer to Appendix C).

7.6.2 Vital Signs

Vital signs will be measured pre-dose in accordance with the Schedule of Assessments (Table 11-1) and should include systolic and diastolic blood pressure, heart rate, respiratory rate, height, weight, and body temperature (to be collected in an age appropriate fashion, e.g., orally, axillary, auricularly, etc.).

At PK time points, vital signs should be assessed as indicated in the Schedule of Assessments (Table 11-1), prior to actual PK blood sampling at these time points.

7.7 Electrocardiograms

Twelve-lead resting ECGs will be performed in accordance with the Schedule of Assessments (Table 11-1). To minimize variability, it is important that patients are in a resting position for at least 5 minutes prior to each ECG evaluation. Body position should be consistently maintained for each ECG to prevent changes in heart rate. ECGs for each patient should be obtained from the same machine whenever possible. When ECGs coincide with PK draw days, ECGs should be performed before the PK blood draw. Any clinically significant changes in ECGs that occur

during the study should be reported as an AE in the eCRF. If the machine generated ECG results include a prolonged QTc interval, the ECG should be interpreted by a qualified health care provider. Electrolytes should be monitored and repletion prescribed as needed (potassium should z≥) D)× U <d)y ≤)L)mdf)y ≤)× y– ≥ " ×)y ≤)• y,,• " ×) — ,,≤)z≥) "—") × y,,),,"× " 5:

7.8 Growth Plate Evaluation

Patients who have not yet obtained full adult height will undergo either X-ray or MRI of the right knee at baseline and every 6 months during participation in the study while the growth plate remains open. Premature closure of the growth plate after study baseline will be captured as an AE.

If it is unclear that a patient has obtained full adult height, a pre-treatment tibial X-ray (anterior posterior and lateral views) or MRI of the right knee should be obtained. Either tibial X-ray or MRI (same modality as baseline) will be performed if the growth plate remains open, every 6 months during participation in the study until the growth plate closes.

7.9 Dental Evaluation

Patients aged 5 years and older, without a full set of permanent teeth, will undergo a dental evaluation at baseline and every 6 months during participation in the study. Patients who enroll prior to their 5th birthday will start dental assessments at the cycle visit closest to their 5th birthday. Detrimental changes in tooth development considered significant after study baseline will be captured as an AE, and will require dentist evaluation.

Patients who enroll with a full set of permanent teeth will not need to undergo dental evaluations.

7.10 Pubertal Maturation Evaluation

Patients aged 7 years and older will be assessed for pubertal maturation every 6 months during participation in the study based on the Tanner Scale. Patients who enroll prior to their 7th birthday will start assessment at the cycle visit closest to their 7th birthday. Delays to pubertal maturity (according to the Tanner Scale) after study baseline will be captured as an AE.

Patients who have completed puberty according to the Tanner Scale at enrollment will not undergo evaluation.

7.11 Laboratory Tests

For all laboratory testing, institutional guidelines for the use of anesthetics prior to venipuncture and maximum number of attempts may be implemented. Age specific maximum blood volume will be adhered to for patients enrolled, per guidance and individual institutional practice. Laboratory normal ranges by age group and by individual institutional reference will guide individual laboratory result assessments.

7.11.1 Pregnancy Test

Pregnancy testing (serum or urine) should be conducted in accordance with the Schedule of Assessments (Table 11-1). Pregnancy reporting information is provided in Section 8.5. Urine or serum pregnancy test are required for female participants of child-bearing potential (surgically sterilized females or those who have not experienced menses for at least 2 years are not required to be tested). If any urine pregnancy test is positive, study treatment will be delayed until the patient pregnancy status is confirmed by a serum pregnancy test. If serum pregnancy test is positive, the patient will be permanently discontinued from study treatment.

7.11.2 Hematology

Hematology should be assessed in accordance with the Schedule of Assessments (Table 11-1) and should include assessment of the following: Hemoglobin, hematocrit, RBC count, WBC count with differential (neutrophils [absolute count and percent] and lymphocytes, monocytes, eosinophils, basophils [percent]) and platelet count.

7.11.3 Serum Chemistries

Serum chemistries (non-fasting) should be assessed in accordance with the Schedule of Assessments (Table 11-1) and should include assessment of the following: alkaline phosphatase, albumin, ALT, AST, BUN or urea, creatinine, glucose, LDH, total and direct bilirubin, total protein, phosphorus, sodium, potassium, chloride, calcium, magnesium, and bicarbonate.

7.11.4 Urinalysis

Urinalysis should be conducted in accordance with the Schedule of Assessments (Table 11-1). Dipstick evaluation may be used if allowed per local standards, but if abnormal, it should be followed up with a complete urinalysis, including color, specific gravity, pH, glucose, bilirubin, ketones, occult blood, protein, leukocytes, nitrites and urobilinogen. If +2 protein is observed; a 24-hour urine collection or urine protein: creatinine (UPC) ratio will be taken to quantify proteinuria.

7.11.5 Calcitonin, Thyroglobulin and Carcinoembryonic Antigen

In patients with MTC, calcitonin, thyroglobulin, and CEA should be assessed in accordance with the Schedule of Assessments (Table 11-1). 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.

7.11.6 Cortisol and Adrenocorticotropic Hormone

In [illegible] **only**, serum cortisol, serum adrenocorticotropic hormone (ACTH) should be assessed in accordance with the Schedule of Assessments (Table 11-1).

7.11.7 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 and 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.

7.12 Pharmacokinetic Samples: Blood (and Cerebrospinal Fluid, if Appropriate)

Blood plasma samples for PK assessments (Phase 1 and Phase 2) will be collected in accordance with the Schedule of Assessments (Table 11-1) and the Schedule of Pharmacokinetic Sampling (Table 11-2). The dose of selpercatinib should be taken in the clinic on PK sampling CCI [redacted] Samples will be collected and handled as outlined in the Laboratory Manual. The PK data collected CCI [redacted] will be used to determine parameters such as area under the concentration versus time curve from time 0 to t (AUC_{0-t}) and plasma terminal elimination half-life ($T_{1/2}$). As noted in Table 11-2, PK samples will also be collected for patients participating in the optional alternate formulation assessment.

If patients have an Ommaya Reservoir or are undergoing diagnostic LP, CSF will also be collected for CCI [redacted] For patients undergoing diagnostic LP, a peripheral blood sample should be taken at the same time as the CSF collection. It is preferred, but not required, that the CCI [redacted]

7.13 Disease Assessment

7.13.1 Tumor Measurements

Disease assessment should be conducted in accordance with the Schedule of Assessments (Table 11-1) and the Imaging Manual Tumor(s) will be assessed by radiographic tumor measurements using standard of care imaging modalities (CT and/or PET) or MRI of chest, abdomen, and pelvis, and any other areas with suspected disease involvement. Patients with a history of, or clinical suspicion of, CNS metastases should additionally have a head CT (or CT / PET) or MRI scan performed at each tumor assessment. Patients with locally advanced disease should have an MRI or CT (or CT / PET) of the site of disease and a CT (or CT / PET) or X-Ray of the chest, plus any other areas of disease involvement. A CT (or CT / PET) or MRI of the chest/abdomen/pelvis should be repeated yearly (or more frequently for clinical concerns) if there is no evidence of disease at baseline. Patients with neuroblastoma will be followed with MIBG scans, anatomic imaging, and bilateral bone marrow aspirates and biopsies. Patients with

MIBG non-avid disease may undergo fluorodeoxyglucose-PET assessment instead of MIBG per International Neuroblastoma Response Criteria guidelines and with sponsor approval.

Investigators should use the same method consistently for an individual patient throughout the study. Disease assessments will utilize RECIST v1.1 (refer to Appendix E, Table 11-7 and Table 11-8); additional details are provided at www.recist.com/). Assessments of brain disease will be made using the current version of RANO Criteria (Appendix F, Table 11-9).

Tumor measurements are to be performed for all patients during Screening. Tumor will be assessed by CT or CT / PET or MRI of chest, abdomen/pelvis, as indicated. Patients enrolled with a history of CNS metastases should additionally have a head CT (or CT / PET) or MRI scan performed at each tumor assessment. Thereafter, tumor measurements and disease response assessments are to be performed for patients known to have measurable disease on Day 1 of every other cycle, starting in Cycle 3 through Cycle 12; thereafter tumor measurements and disease response assessments should be performed on Day 1 (or within 1 week prior) of every third cycle (prior to Day 1 of Cycle 14, 17, 20, etc.). In addition, there is an optional assessment on Day 1 of Cycle 2. Such assessments also are to be performed at the End of Treatment visit if they had not been performed within the previous 2 cycles. Subsequent assessments should use the same radiographic methods as used during Screening.

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 should be maintained at the study center and 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.

7.13.1.1 Collection of Radiographic Studies for Independent Review

Baseline Screening radiographic studies and all subsequent radiographic studies with any clinical information imperative to accurate radiographic assessment of disease will be collected and stored for future independent radiological review. Independent radiology review for this trial is used to assess the objectives of the study and any unexpected medical findings identified during subsequent independent radiologic review. Identification of radiographic findings which may impact patient management or outcomes during the course of patient participation in the study are the responsibility of the treating physician.

7.13.2 Correlative studies: CCI [redacted]

At the time of relapse, CCI [redacted] samples may be obtained, if possible, CCI [redacted]

Whole blood for analyses of CCI [redacted] should be obtained in accordance with the Schedule of Assessments (Table 11-1) (within 7 days following radiologic disease assessment, except for baseline/Screening when it may be obtained any time prior to treatment on C1D1) and with the Laboratory Manual. Whole blood for CCI [redacted]

should be obtained at the EOT visit even if radiologic disease assessment is not performed. Sites may draw fewer tubes based on local institutional policy for maximal blood draws in patients.

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. All specimens will be deidentified and stored at a secure facility designated by the sponsor for up to 15 years from the date of receipt.

7.13.3 Pain and Health-Related Quality of Life: Wong-Baker Faces Scale and PedsQL-Core

Pain and HRQoL assessments should be obtained in accordance with the Schedule of Assessments (Table 11-1). For assessment of pain, patients 3 year of age or older will be assessed using the Wong-Baker Faces Scale. For assessment of HRQoL, all patients will be assessed using the PedsQL-Core for the patient or their parent/caregiver. Each questionnaire should be performed before the patient learns the results of his or her restaging.

7.13.4 Telephone Follow-up

The site will contact the patient by telephone in accordance with the Schedule of Assessments (Table 11-1) to assess for tolerability, continuation of study drug, and whether the patient needs to return to 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.

7.13.5 Survival Status

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

7.14 Study Drug Administration and Dosing Diary

Study drug should be administered in accordance with the Schedule of Assessments (Table 11-1) and Section 5.

BSA should be calculated on Day 1 of each cycle to confirm dose. Dose should be increased for any change in BSA conferring a greater than 10% change in dose (for all cohorts). The maximum dose (regardless of BSA calculation) will be no higher than the recommended adult dose associated with the BSA-based dosing, i.e., patients in Dose Cohort 1 will receive a dose no higher than 160 mg BID, patients in Dose Cohort 2 will receive a dose no higher than 200 mg BID.

Completion of the outpatient dosing diary will include recording of selpercatinib dosing, H2 blockers, and antacids. The diary will be required during Cycles 1-3 and as otherwise instructed (during alternative formulation assessment),and may be used in additional cycles if helpful to the patient/caregiver.

7.14.1 Formulation Acceptability and Palatability Assessments

During the assigned CCI dosing period for selected study subjects (participants) and/or caregivers who give consent, responses to questions designed to assess the acceptability of the CCI formulation (Kozarewicz 2014) will be collected. The questionnaire for the CCI CCI will assess the participants ability to swallow the drug product as intended.

The acceptability questionnaire for the CCI will assess CCI

The appropriate questionnaire(s) will be administered within approximately 30 minutes of dosing after the first dose of the CCI formulation and again after approximately 2-4 weeks of dosing the CCI formulation.

The questionnaire will be completed by caregivers (proxy) for participants aged <6 years. For participants ≥6 years old to <12 years old, both participant and caregiver will complete the questionnaires. For participants ≥12 years old, the questionnaire will be self-completed. In the event a participant aged ≥6 years old cannot complete the questionnaire (i.e., limited capability), the caregiver may complete the questionnaire for the participant (only one questionnaire would need to be submitted for participants ≥6 to <12 years old in this case). This will not be a protocol deviation. Similarly, if the caregiver is the one preparing the CCI, the caregiver and participant should both complete the questionnaire (two questionnaires would be submitted for participants ≥12 years old in this case).

7.15 Concomitant Medication

Concomitant medications should be recorded in accordance with the Schedule of Assessments (Table 11-1).

All medications that were used from 14 days prior to enrollment through the end of study treatment will be recorded in the eCRF. These are to include prescription and nonprescription medications, transfusions, vitamins and nutritional supplements, and other remedies. Excluded prior medications are excluded via the eligibility criteria (Section 4.2). Additional guidance regarding concomitant medications is provided in Section 5.3.

7.16 Adverse Events/Serious Adverse Events

Adverse events (AEs) should be recorded in accordance with the Schedule of Assessments (Table 11-1) and Section 7.20.

7.17 End of Treatment Visit

End of treatment (EOT) is defined as Day 28 (±7 days) of the final cycle of treatment (or time of premature discontinuation of treatment). The EOT assessments and procedures will be conducted in accordance with the Schedule of Assessments (Table 11-1) unless withdrawal of consent occurs prior to scheduled EOT visit.

An optional tumor tissue sample from patients who experienced PD is requested; tissue biopsy collected at EOT visits is optional.

7.18 Safety Follow-up Visit

The safety follow-up assessments will be conducted in accordance with the Schedule of Assessments (Table 11-1). Safety follow-up procedures 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.

Serum chemistries and urinalysis should be assessed only if treatment-emergent abnormalities were seen at EOT.

Status of unresolved AEs should be assessed and may be done by phone if patient is not able to return to clinic.

7.19 Long-Term Follow-up

The LTFU assessments and procedures will be conducted in accordance with the Schedule of Assessments (Table 11-1). After treatment discontinuation, LTFU will occur approximately every 3 months (±1 month) until the patient experiences PD, withdraws consent for further participation, is lost to follow-up, has died, or close of the study. The site will contact the patient follow-up assessments that may include: Date of PD, subsequent anticancer therapy(ies) and survival status. SAEs reported by patients that the Investigator considers related to study drug and that occurred in the follow-up period must be reported to the Sponsor until the patient discontinues from the study (for any reason) or the study closes. 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.

Special considerations: Patients who receive study drug in a pre-surgical fashion and then hold study drug due to histologically negative margins at resection (as is permitted by this protocol) may be considered for re-start of study drug if there is disease recurrence. Therefore, these patients should continue radiographic and/or clinical assessment of disease response utilizing the same modality used at baseline imaging. These response assessments should be collected and reported every 3 months. End of treatment, Safety Follow-up and Long-Term Follow-up visit(s) requirements will be conducted as described in Sections 7.17, 7.18, and 7.19. If disease recurrence is suspected and the Investigator wishes to consider the patient for a re-start of selpercatinib, a conversation with the Sponsor will be required prior to initiation of study drug.

If a patient discontinues study treatment for reasons other than PD, lost to follow-up, withdrawal of consent or initiation of a new anticancer therapy(ies), the patient is required to undergo disease assessment by imaging (utilizing the same modality[ies] used for the baseline imaging assessment) as specified in Section 7.13.1 until PD (even if PD occurs after 2 years), lost to follow-up, withdrawal of consent, or initiation of a new anticancer therapy(ies).

7.20 Continued Access

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

8 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, complaints, or symptoms that occur from the time informed consent is signed until the SFU are to be recorded on the appropriate eCRF (events that occur prior to consent are
• [illegible] 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.

Disease progression of the primary tumor in and of itself is captured as an efficacy assessment and should not be captured as an AE (including fatal AEs) unless the disease progression is assessed as related to study treatment. If toxicities due to disease progression exist and are new or worsened from baseline, these should be reported as AEs. If a new primary malignancy appears, it will also be considered an AE.

8.1 Grading and Intensity of Adverse Events

The Investigator will grade the severity of each AE using, when applicable, the NCI-CTCAE, version 5. In the event of an AE for which no grading scale exists, the Investigator will classify the AE as mild, moderate, severe, life-threatening/debilitating, or fatal, as defined below.

Table 8-1 NCI-CTCAE Definitions of Severity for Adverse Reactions

Toxicity	Grade / Details
Grade 1	**Mild**; asymptomatic or mild symptoms; clinical or diagnostic observations only; no interventions required (an event that is usually transient in nature and generally not interfering with normal activities)
Grade 2	**Moderate**; minimal, local or non-invasive intervention indicated; some limitation of activities (an event that is sufficiently discomforting to interfere with normal activities)
Grade 3	**Severe or medically significant, but not immediately life-threatening**; hospitalization or prolongation of hospitalization required; disabling; limitation of patient's ability to care for him/herself (an event that is incapacitating with inability to work or do usual activity, or inability to work or perform normal daily activity)
Grade 4	**Life-threatening consequences**; urgent intervention required (an event that puts the patient at immediate or potential risk of death, requires [illegible] being)

Toxicity	Grade / Details
Grade 5	**Death related to adverse event** (fatal)

Abbreviations: NCI-CTCAE = National Cancer Institute-Common Terminology Criteria for Adverse Events.

8.2 Relationship to Study Drug

The Investigator will categorize each AE as to its potential relationship to investigational product using the categories of Yes (causally related) and No (unrelated) as defined below. The assessment of the relationship of an AE to the administration of investigational product is a clinical decision based on all available information at the time.

No:
The time course between the administration of study drug and the occurrence or worsening of the AE rules out a causal relationship and another cause (concomitant medications, therapies, complications, comorbidities, etc.) is suspected.

Yes:
The time course between administration of investigational product and the occurrence or worsening of the AE is consistent with a causal relationship and no other cause (concomitant drugs, therapies, complications, comorbidities, etc.) can be identified.

The following factors should also be considered:

Temporal sequence from treatment

Underlying, concomitant, or intercurrent diseases

Concomitant medications

Clinical and/or preclinical data regarding whether a particular response is a class effect

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.

8.3 Serious Adverse Event Reporting

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

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.

(Note: 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.)

All SAEs occurring from the time the ICF and Pediatric Assent Form, where applicable, are signed through 28 days after the last dose should be reported immediately but in no more than 24 hours of the knowledge of the occurrence (this refers to any AE that meets any of the aforementioned serious criteria) to Medpace Clinical Safety. All SAEs that the Investigator considers related to study drug occurring after the 28-day follow-up period must be reported to the Sponsor until the patient discontinues the study (for any reason) or the study closes.

To report the SAE, complete the paper SAE form located in the Study Binder. Fax the completed paper SAE form to Medpace (the fax number is listed below) within 24 hours of awareness.

Safety Contact Information:

Medpace Clinical Safety: U.S. and Asia/Pacific

SAE Reporting Number: Telephone: PPD

Safety Fax: PPD

e-mail: PPD

Medpace Clinical Safety Europe / non-U.S.:

SAE Reporting Number: PPD

Safety Fax: PPD

e-mail: PPD

Within 24 hours of receipt of new information, the updated follow-up SAE form, along with any supporting documentation (e.g., patient discharge summary or autopsy reports), should be faxed or emailed as noted above.

The Investigator will be requested to supply detailed information regarding the event. SAEs should be reported to the Institutional Review Board (IRB)/Research Ethics Board (REB)/Independent Ethics Committee (IEC)/Human Research Ethics Board (HREC) 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 (after obtaining the necessary signed informed consent from the pregnant female partner directly) who becomes pregnant during a clinical study.

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) of the primary tumor in and of itself is captured as an efficacy assessment and should not be captured as an AE or an SAE (refer to Section 7.20).

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.

8.4 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) z ≥ ≥)• ≥) “;) —≥)kQU)—y) resolved, or until the condition stabilizes or is deemed chronic (in the case of persistent impairment), or the patient dies.

8.5 Pregnancy Reporting

If the patient, or the partner of a patient (after obtaining the necessary signed informed consent from the pregnant female partner directly) 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.

9 PLANNED ANALYSES

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

9.1 Study Endpoints

9.1.1 Phase 1 Study Endpoints

9.1.1.1 Primary

The primary endpoint for Phase 1 is the frequency, severity and relatedness of TEAEs and SAEs, including DLTs in pediatric patients receiving selpercatinib.

9.1.1.2 Secondary

The secondary endpoints for Phase 1 are:

- 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}), maximum drug concentration (C_{max}), time to maximum plasma concentration (T_{max}), degree of accumulation, and other characterizations
- The MTD and/or the RP2D of selpercatinib in pediatric patients
- ORR and CBR based on RECIST 1.1 or RANO as appropriate to tumor type as determined by an IRC and treating investigator

9.1.2 Phase 2 Study Endpoints

9.1.2.1 Primary

The primary endpoint for Phase 2 is the ORR based on RECIST v1.1 or RANO in pediatric patients with tumors harboring an activating RET alteration as appropriate to tumor type determined by IRC.

9.1.2.2 Secondary

The secondary endpoints for Phase 2 are:

- ORR based on RECIST v1.1 or RANO as appropriate to tumor type per the treating Investigator's response assessment
- DOR (IRC and treating Investigator)
- PFS (IRC and treating Investigator)
- OS
- CBR (IRC and treating Investigator)
- 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}, T_{max}, degree of accumulation, and other characterizations
- The percent positive agreement between prior molecular profiling that detected a RET alteration within the patient's tumor with diagnostic test(s) being evaluated by the Sponsor
- Post-operative staging and surgical margin status in patients who have definitive surgery following treatment with selpercatinib
- Change from baseline in patient-reported pain at BOR visit as assessed by the Wong-Baker Faces Scale.
- Assessment of CCI including palatability (if applicable)

CCI

9.2 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.

Safety Analysis Set (SAS)

The SAS will be used primarily for the analysis of safety data and will consist of all enrolled patients who receive at least 1 dose of selpercatinib. The SAS will also be used for the analysis of efficacy data unless otherwise specified.

9.3 Determination of Sample Size

9.3.1 Phase 1

A minimum of [redacted] patients would be required to be enrolled into a dose escalation cohort 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 before declaring an MTD or RP2D. 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.

If an investigative site identifies a patient with a known RET alteration, the patient may be enrolled to a previous cohort that has been determined safe after discussion with the Sponsor's Medical Monitor. If a patient with a RET alteration is identified after [redacted] patients have been enrolled on Dosing Cohort 1, and prior to clearance of the DLT window, that patient will be enrolled to Dose Level -1. Following clearance of Dose Level 1, the patient(s) enrolled to Dose Level -1 may be escalated to Dose Level 1 upon discussion between the Investigator and the Sponsor's Medical Monitor. Patients who miss 7 or more days of dosing in Cycle 1 for reasons unrelated to study drug toxicity will be considered to have inadequate study drug exposure to support dose escalation and will be replaced.

9.3.2 Phase 2

The number of patients planned for each Phase 2 cohort was determined largely by feasibility considerations owing to the extreme rarity of pediatric with an advanced cancer harboring an activating RET alteration. Cohorts 1 and 2 may enroll approximately 10-20 patients. Although the planned sample size is limited, it is anticipated that the objective response rate may be high

4 50%) for each cohort evaluated. For Cohorts 1 and 2, a sample size of 20 patients is estimated to provide approximately 75% power to achieve a lower boundary of a two-sided 95% exact binomial confidence interval (CI) about the estimated ORR that exceeds 20%. Ruling out a lower limit of 20% is considered clinically meaningful in patients who have limited treatment options for their advancing disease. Cohorts 3-4 are anticipated to enroll too few patients to be powered for a formal statistical testing.

9.4 Demographics and Baseline Characteristics

Descriptive summaries of demographic and baseline characteristics for all enrolled patients will be presented by study phase. For the Phase 1 portion, tabulations will be provided by dose cohort and overall as appropriate. For Phase 2, tabulations will be provided by cohort and overall as appropriate.

9.5 Safety Analyses

Safety will be assessed by clinical review of all relevant parameters including AEs, SAEs, laboratory values, and vital signs. Unless specified otherwise, the safety analyses will be conducted for the safety population defined in Section 9.2. Tabulations will be provided by dose cohort and overall summary across both Phase 1 and Phase 2.

9.5.1 Assessment Committee

The Sponsor will appoint an Assessment Committee (AC) to include, a global principal investigator, an external — “•“y 8)—≥)) ”≥•) — “•“y)y ≤)—≥))• × ≤) lead statistician. The AC will determine whether the study should continue as planned, or whether modifications, such as protocol amendments for example to change enrollment, or patient monitoring are warranted. The first AC meeting will be performed after 10 patients have been enrolled and had the opportunity to be treated for 2 cycles. The AC will then meet and review safety data approximately every 6 months subsequently, until enrollment closure, then annually.

9.5.2 Safety Review Committee

A Safety Review Committee (SRC), separate and in addition to the AC, 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 k)e ≥“•y,,)e “ 8y)S,,“ “•y,,)g ≥y“)≥ ≥≥ y“ ≥8y ≤)—≥)h “ •“ y,,)a ≥ “–y) (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 at a minimum of every 6 months (or more frequently depending on enrollment or observed safety profile). Decisions will be documented in written minutes.

9.5.3 Treatment Emergent Adverse Events

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 a standardized preferred term using the Medical Dictionary for Regulatory Activities (MedDRA), version 21.1 or later.

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 8.3. 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:

TEAEs by any grade, and Grade 3/4/5

Drug-related TEAEs by any grade, and Grade 3/4/5

TEAEs with action of study drug delayed/interrupted or dose reduced

TEAEs with action of study drug discontinued

Treatment-emergent SAEs

Drug-related treatment-emergent SAEs

Fatal/Grade 5 TEAEs

9.5.4 Dose-Limiting Toxicity

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 confidence interval (CI).

9.5.5 Deaths

All deaths on study should be reported and recorded. All deaths that occur on study will (to the z≥) √) –≥)k)yz“;“ 5 be reported in a patient listing and will include the primary cause of death and the number of days between the date of the last dose of study drug and death.

9.5.6 Laboratory Values

Laboratory values will be assigned toxicity grades when available using the NCI-CTCAE, version 5. Directional shifts in laboratory toxicity grades (comparing baseline grade with worst postbaseline 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.

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 postbaseline value

Maximum postbaseline value

Average postbaseline value

Last postbaseline value

9.5.7 Vital Signs

All patients will have pretreatment baseline vital signs and pre-dose measurements on Day 1 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 postbaseline value will be determined relative to the baseline vital sign measurements only.

9.5.8 Concomitant Medications

Prior and concomitant medications will be coded to the generic term using World Health Organization (WHO) Drug Dictionary version September 2018 or later and will be summarized by generic term and listed by patient.

9.6 Efficacy Analyses

The efficacy analyses will be conducted on the SAS unless otherwise specified. The efficacy outcomes for patients enrolled in the Phase 1 and Phase 2 will be summarized by cohort or by tumor type, and overall, as appropriate.

ORR and CBR will be estimated using disease-specific response criteria (e.g., RECIST v1.1 for patients with solid tumor or RANO for patients with primary CNS tumors). The ORR will be calculated as the proportion of patients with best overall response (BOR) of complete response (CR) or PR. The CBR will be calculated as the proportion of patients with BOR of CR, PR, or SD lasting 16 or more weeks following initiation of selpercatinib. All responses will be confirmed by a second scan 28 days after the initial response. The estimate of the ORR and CBR will be accompanied by 2-sided 95% CI. The primary analysis of ORR will be based on the responses determined by an IRC. A secondary analysis of ORR will be based on the treating a ≥ “–y)y ≥ ×≥ : CBR will also be analyzed based on the IRC and the treating investigator as a secondary endpoint.

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 recurrence or PD is objectively documented. If a patient dies, irrespective of cause, without documentation of recurrent or PD beforehand, then the date of death will be used to denote the response end date.

PFS is defined as the number of months from the date of the first dose of study drug to the earliest of documented PD or death with or without evidence of prior progression. PFS events occurring during a Sponsor-approved drug holiday will be included as events for PFS and DOR (will not be censored).

OS is defined as the number of months from the date of the first dose of study drug to the date of death (due to any cause).

Time-to-event (TTE) endpoints (DOR, PFS and OS) will be summarized descriptively using the Kaplan-Meier method. The Kaplan-Meier estimate with 95% CI calculated using Brookmeyer and Crowley method will be provided for the median. The event-free rate with the 95% CI calculated using Greenwood's formula will be provided for selected time points. Median follow-up for each endpoint will be estimated according to the Kaplan-Meier estimate of potential follow-up (Schemper and Smith 1996).

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

- Patients with no baseline or postbaseline disease assessments unless death occurred prior to the first planned assessment (in which case the death will be considered an event).
- Patients who initiate subsequent anticancer therapy in the absence of documented progression.
- 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 progression-free on or before the data cut-off date.

For such patients, the progression or censoring date will be determined based on described conventions (Food and Drug Administration 2007). Detailed censoring scheme is described in the SAP.

9.7 Pharmacokinetic Analyses

Plasma and CSF concentrations of selpercatinib will be determined with a validated bioanalytical assay. Refer to Section 7.12.

PK parameters such as C_{max} and AUC will be calculated when feasible. Summary statistics will be generated by dose cohort and across cohorts as appropriate. Samples of plasma may also be analyzed for the presence of metabolites of selpercatinib; if such analyses are conducted, they will be reported separately by the Sponsor. Additionally, the CCI [redacted]

9.8 Pain and Health Related Quality of Life

Quality of completion will be assessed at each study visit based on the number of completed assessments divided by the number of expected assessments, defined as the number of patients eligible to complete each patient-reported outcome instrument at that visit.

In patients 3 years of age or older, pain will be assessed by the Wong-Baker Faces Scale. CCI [redacted] Change from baseline in patient-reported pain will be calculated at the BOR visit. CCI [redacted]

The HRQoL assessment will be based on the PedsQL-Core for the patient or their parent/caregiver. CCI [redacted]

CCI [redacted]

[redacted] will be reported along with 95% CI by Clopper-Pearson.

10 STUDY ADMINISTRATION

10.1 Regulatory and Ethical Considerations

10.1.1 Regulatory Authority Approval

This study will be conducted in accordance with the standard of Good Clinical Practices (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/REB/IEC/HREC has reviewed and approved this protocol prior to initiating the study. The Investigator must provide the k))k) ≥ ≥ ≥ y " ≥ with current and revised IRB/REB/IEC/HREC × ≥× z≥ —") ≥) —y)" •,, <>) —≥)× ≥× z≥) •• y ")y ≤)qualifications or provide a copy of the United States Department of Health and Human Services Assurance Number.

The IRB/REB/IEC/HREC ×)y,,) ≥ "≥)y ≤)y ≥) —≥)•,," "•y,,) "≥ ICF, Pediatric Assent Form, 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/REB/IEC/HREC approval(s) prior to the start of the study.

The IRBs/REBs/IECs/HREC are required to determine if child assents are appropriate for all studies that include pediatric patients. The IRB/REB/IEC/HREC may opt to waive assent if the patients are not capable of understanding (e.g., based on level of intellectual development or maturity) or if the study is in the best interest of the patient (i.e., strong possibility of benefit and no other alternatives are available). If an IRB/REB/IEC/HREC chooses to waive assent, this must be documented in the IRB/REB/IEC/HREC approval letter.

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

10.1.3 Patient Informed Consent and Pediatric Assent

The Investigator and designated site staff who will perform the consent/assent process are responsible for knowing country-specific regulations and other local requirements with regard to child assent to ensure that the assent process is conducted in accordance with those requirements. 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),≥—y,,,)y••≥ yz,≥) ≥ ≥ ≥ y " ≥8)legal

guardian, or impartial witness. Written informed consent and pediatric assent, where applicable, must be obtained prior to the patient entering the study (before initiation of any study-related Screening procedure). In pediatric cases, where applicable and according to local regulations, both parents may be required to sign informed consent. Sufficient time will be allowed to discuss any questions raised by the patient. The ICF/Pediatric Assent Form, which will contain all International Conference on Harmonisation (ICH)-required elements and local privacy authorization information in a language that is understandable to the patient, must be signed by all patients, or by the patient's legal representative. The process of obtaining the ICF and Pediatric Assent Form, where applicable, will be in compliance with all applicable local and country regulations and ICH requirements.

The Pediatric Assent Form must have a date and signature line for the child. Regional laws differ in their requirements for patients who have not reached the legal age of majority and IRBs/REBs/IECs/HRECs are responsible for following their local regulations. Use of an assent is not a substitute for parental permission. Parents/guardians must receive a full ICF to review and sign.

If the ICF and Pediatric Assent Form, where applicable, is amended during the study, the Investigator must follow all applicable regulatory requirements pertaining to IRB/REB/IEC/HREC approval of the amended form. The clinical site must use the amended ICF/ Pediatric Assent Form for all new patients and repeat the consent/assent process with the amended form for any ongoing patients.

An initial ICF (for adult patients or parent/guardian of child/adolescent patients) and Pediatric Assent Form (for child/adolescent patients, as applicable) will be provided to the Investigator to ≥ y ≥) –≥)aS V)y ≤)y ≥)≤ • × ≥))z≥) ≍)y) –≥)ha) “≥:)The sample ICFs/Pediatric Assent Forms prepared by the Sponsor are provided in the Study Manual.

10.1.4 Investigator Reporting Requirements

In accordance with applicable regulatory requirements, the Investigator is solely obligated to inform the IRB/REB/IEC/HREC of progress of the study and notify the IRB/REB/IEC/HREC of study closure. The Investigator must also provide the Sponsor with copies of all IRB/REB/IEC/HREC correspondence that relate to study approvals, updates, or changes. The Investigator is also responsible for forwarding to the IRB/REB/IEC/HREC reports of any SAEs from other studies conducted with the same investigational product that were provided by the Sponsor.

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

10.2 Data Management

T y y) “,,)z≥) ≥• ≤≍)y) –≥) “≥)) •≥)≤ • × ≥)y ≤) ≥ “≥ ≍)z) –≥)k)monitor during periodic visits, who will verify data recorded on the eCRFs within the Clinical Database Management System (CDMS) in accordance with source documents. All updates, corrections or changes made to study data must be appropriately tracked in an audit trail in the CDMS. The

eCRFs will be considered complete when all missing, incorrect, and/or inconsistent data has been accounted for. Additional instructions on eCRF completion are provided in the eCRF Completion Guidelines.

All eCRFs must be reviewed and patient casebooks signed by the Investigator according to CDMS specifications.

10.2.1 Data Protection

hy "•" y) ",,)z≥)y "– ≍≤)y) " ≥)"≤ "√≥)z) –≥))) ≥•) –≥) y "•" y) 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.

l –≥) y "•" y)×)z≥)" √ × ≍≤) –y) –≥) y "•" y) ≥ y,,) ≤ -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 y ≤) •≥ ≥ :)l –≥)) •≥ ≥)y ≥)• × ,,"y) "–), •y,,) " y•),y)y ≤) ≥,≥ y) legislations including the General Data Protection Regulation (GDPR).

10.3 Study Monitoring

h "))–≥) y) √)–≥) ≤ 8)–≥)k)× ")or designee will contact the clinical site to discuss the protocol and data collection procedures and conduct applicable training of site personnel. The Sponsor and its designees will also periodically contact the clinical site during the conduct of the study (which will include on-site visits) in accordance with applicable regulations and GCP. During these contacts, the monitoring activities will include:

Checking and assessing the progress of the study

Reviewing study data collected to date for completeness and accuracy

Conducting source document verifications by reviewing each patient)Sj V)y–y") •≥) 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/REB/IEC/HREC 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, GCP, and all applicable regulatory requirements. Additionally, to ensure compliance with 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 study 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/REB/IEC/HREC 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 y•• ≤y •≥) "—) —≥)k) •≍ res.

Communication of Suspended or Terminated Dosing

If a decision is taken to suspend or terminate dosing in the trial due to safety findings, this decision will be communicated by Lilly to all investigators (for example, by phone and/or email) as soon as possible. It will be a requirement that investigators respond upon receipt to confirm that they understand the communication and have taken the appropriate action prior to further dosing any participants with study intervention. Any investigator not responding will be followed up by Lilly personnel prior to any further planned dosing. If a dose is planned imminently, Lilly personnel will immediately, and continually, use all efforts to reach investigators until contact is made and instructions verified.

Reports

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

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. 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.

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Appendix A Study Assessments

Table 11-1 Schedule of Assessments

Evaluation	Screening	28-Day Cycles			End of Treatment (EOT)	Safety Follow-Up	Long- Term Follow-Up (LTFU)
		Cycle 1[q]	Cycles 2 through 12	Cycles 13 and Higher			
Visit Window	**(Day -28 to Day 0)**	**± 2 Days**	**± 3 Days**	**± 7 Days**	**± 7 Days**	**Day 28 +7 days**	**Every 3 months ± 1 month**
Informed Consent/Pediatric Assent	X	—	—	—	—	—	—
Medical, surgical, and malignant history	X	—	—	—	—	—	—
Urine or serum pregnancy test (if applicable)*	X	X	X	X	—	—	
Tissue biopsy [a]	X	—	—	—	X	—	—
Physical examination and Karnofsky or Lansky [b]	X	Days 1, 8, 15	Day 1	Day 1[v]	X	X	—
Vital signs [c]	X	Days 1, 8, 15, pre-dose	Day 1 pre-dose	Day 1 pre-dose[v]	X	X	X
CCI [redacted]	[redacted]	[redacted]			[redacted]	[redacted]	[redacted]
12-lead ECG [e]	X	Day 1, 8	Day 1	Day 1[v]	X	X	—
Hematology [f]	X	Days 1, 8, 15	Day 1	Day 1[v]	X	X	—
Serum chemistries [g]	X	Days 1, 8, 15	Day 1, Day 15 (Cycles 2-4) Day 1 (Cycles 5-12)	Day 1[v]	X	[X] [r]	—
Urinalysis [h]	X	Day 1	Day 1	Day 1[u,v]	X	[X] [r]	—
Thyroid Hormone (TSH and T4 or free T4 per local standard)	X		Day 1 of odd cycles beginning with C3	Day 1 of every 3rd cycle starting at Cycle 13[v]			

Evaluation	Screening	28-Day Cycles			End of Treatment (EOT)	Safety Follow-Up	Long- Term Follow-Up (LTFU)
		Cycle 1[q]	Cycles 2 through 12	Cycles 13 and Higher			
Visit Window	**(Day -28 to Day 0)**	**± 2 Days**	**± 3 Days**	**± 7 Days**	**± 7 Days**	**Day 28 +7 days**	**Every 3 months ± 1 month**
Patients with MTC ONLY: Calcitonin, thyroglobulin, CEA	X	Day 1, 8, 15	Day 1	Day 1 of every 3rd cycle starting at Cycle 13[v]	Day 1		Day 1
Patients with MTC (or other cancer y ‘≥) “—)S —“ –)≤“ ≥y ≥5D)k≥ ×) cortisol, serum ACTH	X	Day 1	Day 1	Day 1 of every 3rd cycle starting at Cycle 13[v]			
Growth plate evaluation [i]	X		q 6 months (if patent)	q 6 months (if patent)	q 6 months (if patent)	q 6 months (if patent)	q 6 months (if patent)
Dental evaluation [j]	X		q 6 months (if no full set of permanent teeth)	q 6 months (if no full set of permanent teeth)	q 6 months (if no full set of permanent teeth)	q 6 months (if no full set of permanent teeth)	q 6 months (if no full set of permanen t teeth)
Pubertal maturation evaluation [k]	X		q 6 months until pubertal maturity	q 6 months until pubertal maturity	q 6 months until pubertal maturity	q 6 months until pubertal maturity	q 6 months until pubertal maturity
Menarche (female patients only)	Collect date of menarche as medical history, if applicable	Collect date of menarche if occurs during the course of the study.					
Disease assessment [l]	X		Day 1 (±7 days) Cycle 2 (optional) and odd cycles	Day 1 (±7 days) every third	[X] [s]		X [t]

Evaluation	Screening	28-Day Cycles			End of Treatment (EOT)	Safety Follow-Up	Long- Term Follow-Up (LTFU)
		Cycle 1[q]	Cycles 2 through 12	Cycles 13 and Higher			
Visit Window	**(Day -28 to Day 0)**	**± 2 Days**	**± 3 Days**	**± 7 Days**	**± 7 Days**	**Day 28 +7 days**	**Every 3 months ± 1 month**
				cycle starting at Cycle 14			
Telephone follow-up	—	Day 22	—	—	—	—	—
Pain CCI	X	Day 1 pre-dose	Day 1 pre-dose	Day 1 pre-dose[v]	X	X	—
Whole blood for CCI		Day 1, 15	Day 1 odd cycles to coincide with disease assessment	Every 12 cycles (approx. annually) starting at Cycle 14 to coincide with disease assessment	X	—	—
Whole blood for genomic CCI	X	—	—	—	—	—	—
Selpercatinib administration	—	→	→	→	A	—	—
Patient dosing diary[w]	—					—	—
Patient palatability questionnaire[x] (CCI)	—	—	As directed during alternate formulation assessment		—	—	—
Patient acceptability questionnaire[x] (CCI)	—	—	As directed during alternate formulation assessment		—	—	—
Adverse events [p]	→	→	→	→	→	→	—
Concomitant medications	→	→	→	→	→	→	—

Abbreviations for Table 11-1 and Footnotes: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; AUC_{0-24} = area under the curve time 0 to 24 hours; BUN = blood urea nitrogen; C1D1 = Cycle 1 Day 1; CEA = carcinoembryonic antigen; CCI
CNS = central nervous system; CSF = cerebrospinal fluid; CT = computerized tomography; DLTs = dose-limiting toxicities; DNA = deoxyribonucleic acid; ECG = electrocardiogram; EOT = end of treatment; h = hour; CCI LDH = lactate dehydrogenase; LTFU = long-term follow-up; MIBG = meta-iodobenzylguanidine; MRI = magnetic resonance imaging; PedsQL-Core = Pediatrics Quality of Life - Core Module; PET = positron

emission tomography; PK = pharmacokinetics; RBC = red blood cell; UPC = urine protein: creatinine ratio; WBC = white blood cell; SAE = serious adverse event.

Footnotes for Schedule of Assessments:

[a] Availability of tissue biopsy is required following the most recent progression. If tissue meeting this criterion is not available, a tissue sample obtained prior to most recent progression is acceptable. If neither of these samples are available for submission, then a fresh tumor biopsy is requested if it can be safely obtained. If no tissue is available the patient may still be eligible for enrollment following conversation with the Sponsor. Tissue biopsy collected at the EOT visit is optional. Additional biopsies may be requested on a case-by-case basis in patients re-starting study drug following a "drug holiday" and disease recurrence.

[b] Physical examination includes review of systems: breast/chest, extremities, genitourinary, head/ears/eyes/nose/throat, lymph nodes, musculoskeletal, pulmonary, and skin, thorough neurologic assessment, body weight, and height during Screening. Symptom-directed physical and neurological examinations, including measurement of weight and height, will be performed as part of vital signs. Karnofsky should be assessed for those 16 years old or older, or Lansky should be assessed for those younger than 16 years.

[c] **Vital signs on Day 1** should be predose. **Vital signs on Day 8** should be predose and at CCI [redacted] **Vital signs on Day 15** should be Pre-dose. Vital signs in Cycles 2 and beyond should be predose. During LTFU, only height and weight are to be recorded.

[d] **Blood for PK** will be collected as outlined in Appendix B**.**

[e] ECGs should be resting 12-lead ECG performed during Screening and during Cycle 1 at the following time points: pre-dose (±10 minutes, up to 4 hours pre-dose), C1D1 pre-dose and 2 and 4 hours post-dose (±10 minutes), C1D8 pre-dose and 2 and 4 hours post-dose (±10 minutes. In addition, ECGs should be obtained pre-dose and 2 hours post-dose (±10 minutes) on C2D1 and pre-dose Cycles 3-EOT (during cycles when ECG is required). Additional ECGs may be performed if clinically indicated. For intra-patient dose escalation, ECGs should be performed pre-dose (up to 4 hours pre-dose) on Day 1 and 8 of the patient's new dose, at pre-dose, 2 and 4 hours post-dose (±10 minutes).

[f] Hematology will include Hb, hematocrit, RBC count, WBC count with differential (neutrophils [absolute count and percent] and lymphocytes, monocytes, eosinophils, basophils [percent]), and platelet count.

[g] Serum chemistries (non-fasting) will include alkaline phosphatase, albumin, ALT, AST, BUN/urea, creatinine, glucose, LDH, total and direct bilirubin, total protein, phosphorus, sodium, potassium, chloride, calcium, magnesium and bicarbonate.

[h] If performed by dipstick, abnormal results should be followed by a complete urinalysis, including color, specific gravity, pH, glucose, bilirubin, ketones, occult blood, protein, leukocytes, nitrites and urobilinogen. If +2 protein is observed; a 24-hour urine collection or UPC ratio will be taken in order to quantify proteinuria.

[i] Patients who have not yet obtained full adult height will undergo imaging (anterior posterior and lateral views) of the right knee at baseline and every 6 months during participation in the study while the growth plate remains patent. If it is unclear that a patient has obtained full adult height, a pre-treatment tibial imaging (anterior posterior and lateral views) of the right knee should be obtained. If the growth plate remains patent, the patient will have imaging (anterior posterior and lateral views) performed every 6 months during participation in the study until the growth plate is no longer patent.

[j] Patients aged 5 and older, without a full set of permanent teeth, will undergo a dental evaluation at baseline and every 6 months during participation in the study. Patients who enroll prior to their 5th birthday will start dental assessments at the cycle visit closest to their 5th birthday. Changes in tooth development after baseline will be captured as an AE. Patients who enroll with a full set of permanent teeth will not need to undergo dental evaluations.

[k] Patients aged 7 and older will be assessed for pubertal maturation every 6 months during participation in the study based on the Tanner Scale. Patients who enroll prior to their 7th birthday will start assessment at the cycle visit closest to their 7th birthday. Delays to pubertal maturity (according to the Tanner Scale) after baseline will be captured as an AE. Patients who completed puberty according to the Tanner Scale at enrollment will not undergo evaluation.

[l] Tumor will be assessed by standard of care imaging modalities (CT and/or PET) or MRI of chest, abdomen, and pelvis, any other areas with suspected disease involvement. Patients enrolled with a history of CNS metastases should additionally have a head CT or MRI scan performed at each tumor assessment. Patients with locally advanced infantile fibrosarcoma should have an MRI or CT of the site of disease and a CT or X-Ray of the chest, plus any other areas of disease involvement. Patients with neuroblastoma will be followed with MIBG scans, anatomic imaging, and bilateral bone marrow aspirates and biopsies.

[m] CCI will be collectedCCI . In patients 3 year of age or older, pain will be assessed by the Wong-Baker Faces Scale. CCI .

[n] Whole blood for CCI should be obtained within 7 days following radiologic disease assessment, except for baseline/Screening when it may be obtained any time prior to treatment on C1D1. Whole blood for CCI should be obtained at the EOT visit even if radiologic disease assessment is not performed. Patients less than 5 years of age will have 1×10 mL Streck tube drawn. Patients older than 5 years of age will have 2×10 mL Streck tube drawn. Sites may draw fewer tubes based on local institutional policy for maximal blood draws in patients.

[o] Whole blood for CCI should be obtained any time during Screening prior to beginning treatment. Patients greater than 5 years of age will have one PAXGene tube (8.5 mL) drawn. Patients less than 5 years of age will not have any PAXGene tube drawn. Sites may draw fewer tubes based on local institutional policy for maximal blood draws in patients.

[p] Adverse event (AE) reporting should include the reporting of all AEs occurring for 28 days after the last dose of study drug regardless of cause of discontinuation. The reporting of SAEs should occur, according to SAE reporting criteria, until the patient discontinues the study, or the study is closed. Refer to Section 9 Adverse Events.

[q] During Cycle 1, observations will be performed prior to selpercatinib dosing on that day. Unless otherwise indicated, C1D1 evaluations may be performed either on Day -1 or predose on C1D1; if an evaluation is performed on Day -1, it need not be repeated on C1D1. Routine clinic visits performed within ± 2 days of the nominal visit day will not be considered protocol deviations.

[r] Repeat the assessment only if the EOT result showed treatment-emergent abnormalities.

[s] Assessment should be performed if no disease assessment was performed in last 2 cycles.

[t] Date of progression, as assessed by treating Investigator and survival status (may be conducted by phone). Refer to Section 7.19. Patients following LTFU procedures during Drug Holiday (Section 5.2.5) should also have standard of care imaging procedures every 12 weeks.

[u] Perform only as clinically indicated.

[v] Perform at least every 12 weeks after 2 years on treatment. Align with disease assessment visits.

[w] Dosing diary will be required during Cycles 1-3 and during the cycle of alternative formulation (CCI) administration.

[x] Questionnaires will be administered within approximately 30 minutes of dosing after the first dose of the CCI formulation and again after approximately 2 to 4 weeks of alternative formulation (CCI) administration and returned at the following clinic visit.

* Perform more frequently if required by local regulations.

Schedule of On-Study Treatment Activities
For all Cycles:

The changes to procedures described below are temporary measures intended to be used only during specific time periods as directed by the Sponsor in partnership with the Investigator (see Appendix L).

If there is a concern during a remote visit that suggests on-site visit is necessary, the participant should have an on-site follow-up visit as soon as possible.

The following should occur at the investigative site:

- All visits and procedures in Cycle 1
- CCI
- ECG at C2D1 and C3D1
- Serum chemistries at C2D1 and C3D1
- Growth plate evaluation
- Dental evaluation
- Pubertal maturation evaluation
- Disease assessment, and
- Whole blood for CCI

In exceptional circumstances, procedures not listed above may be conducted remotely (see Appendix L). Remote visits should include a virtual visit with the study Investigator (including video) and mobile healthcare in accordance with local regulations if written approval is provided by the Sponsor and according to the preferences of the participant and study site.

Appendix C Karnofsky and Lansky Performance Status Scales

Table 11-3 Karnofsky Performance Score (16 years old)

Score	Karnofsky Description
100	Normal; no complaints; no evidence of disease
90	Able to carry on normal activity; minor signs or symptoms of disease
80	Normal activity with effort; some signs or symptoms of disease
70	Cares for self; unable to carry on normal activity or do active work
60	Requires occasional assistance, but is able to care for most personal needs
50	Requires considerable assistance and frequent medical care
40	Disabled; requires special care and assistance
30	Severely disabled; hospitalization is indicated, although death not imminent
20	Very sick; hospitalization necessary; active support treatment is necessary
10	Moribund; fatal processes progressing rapidly
0	Dead

(Karnofsky and Burchenal 1949)

Table 11-4 Lansky Performance Score (< 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 plan *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

(Lansky, List et al. 1987)

Appendix D Inhibitors and Inducers of CYP3A4

Table 11-5 Inhibitors of CYP3A4

Strong Inhibitors [a]	**Moderate Inhibitors** [b]
Boceprevir	Amprenavir
Clarithromycin	Aprepitant
Conivaptan	Atazanavir
grapefruit / 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; CYP3A = cytochrome P450 3A enzyme.
[a] Increases the AUC of the substrate by 5-fold.
[b] Increases the AUC of the substrate by 2- to 5-fold.

Table 11-6 Inducers of CYP3A

Strong Inducers [a]	**Moderate Inducers** [b]
Avasimibe	Bosentan
Carbamazepine	Efavirenz
Phenytoin	Etravirine
Rifampin	Modafinil
k)b —)	Nafcillin

Abbreviations: AUC = area under the concentration versus time curve; CYP3A = cytochrome P450 3A enzyme.
[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 Tumor Measurements and Assessment of Disease Response: RECIST, Version 1.1

Measurable versus Non-Measurable

Measurable: lesions that could accurately be measured in at least one dimension as 10 mm by CT scan or caliper measurement by clinical examination or 20 mm by chest X-ray; the longest diameter is to be recorded.

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. The sum of the longest diameter for all target lesions is to be calculated and recorded in the CRF as the baseline sum longest diameter.

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 CRF. Measurement of non-target lesions is not required.

Disease response in target and non-target lesions will be assessed by the Investigator using RECIST, version 1.1, according to the categories and criteria described in Table 11-7. 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 11-8.

Table 11-7 Response Evaluation Criteria in Solid Tumors (RECIST) Guidelines for Tumor Response

Disease Response Criteria for Target and Nontarget Lesions	
Evaluation of Target lesions	
Complete Response (CR):	Disappearance of all target lesions.
Partial Response (PR):	At least a 30% decrease in the sum of the LD 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 LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions.
Evaluation of Nontarget lesions	
Complete Response (CR):	Disappearance of all nontarget lesions and normalization of tumor marker level.
Incomplete Response/ Stable Disease	Persistence of one or more nontarget lesion(s) or/and maintenance

(SD):	of tumor marker level above the normal limits.
Progressive Disease (PD):	Appearance of one or more new lesions and/or unequivocal progression of existing nontarget lesions.

Abbreviation: LD = longest diameter.

Source: Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45(2):228-47. Available at: http://www.eortc.be/recist/documents/RECISTGuidelines.pdf

Table 11-8 Overall Response Criteria

Patients with Target and Nontarget 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 Nontarget 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 = not evaluable; PD = progressive disease; PR= partial response; SD = stable disease.

Source: (Eisenhauer, Therasse et al. 2009). Available at : New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45(2):228-47. Also available at: http://www.eortc.be/recist/documents/RECISTGuidelines.pdf

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

The RANO criteria (Wen 2010: https://ascopubs.org/doi/pdf/10.1200/jco.2009.26.3541) 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 11-9 RANO Response Criteria Incorporating MRI and Clinical Factor

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 no 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; MRI = magnetic resonance imaging; 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

Is 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 G Proton Pump Inhibitors (PPIs)

Concomitant use of proton pump inhibitors (PPIs) should be avoided. For patients unable to discontinue use of PPIs, selpercatinib must be administered with a meal.

The information in this table is provided as guidance to investigators and is not considered exhaustive.

Table 11-10 Examples of Proton Pump Inhibitors (PPIs)

Omeprazole
Esomeprazole
Lansoprazole
Pantoprazole
Rabeprazole
Dexlansoprazole

Appendix I Examples of Multikinase Inhibitors with Anti-RET Activity

Table 11-12 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 J Examples of *RET*-Activating Mutations

Table 11-13 Examples of *RET*-Activating Mutations

Exon	RET mutation
5	V292M, G321R
8	A510V, E511K, C515S, C531R, G533C
10	V591I, R600Q, K603E/Q, Y606C, C609F/G/R/S/W/Y, C611F/G/R/S/W/Y, C618F/G/R/S/W/Y, C620F/G/R/S/W/Y
11	C630R/Y, D631Y, E632K, C634F/G/R/S/W/Y, S649L, K666E/M
13	E768D, R770Q, N777S, V778I, Q781R, L790F, Y791F/N
14	V804L, V804M, Y806C, E819K, R833C, R844Q, R866W, M848T
15	L881V, A883F/S/T/V, R886W, S891A, S904F
16	S904C/F, G911D, R912P, M918T, E921K, S922P, T930M
Complex	D631del, E632-L633del, D898-E901del, E632-A639> HR
Other	Because the list of published activating *RET* mutations is constantly being updated, other mutations (e.g., other complex mutations, overlapping deletions, substitutions with different amino acids at the same site) may be eligible if a compelling rationale is provided by the Investigator and approved by the Sponsor.

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

Appendix K Continued Access

Table 11-14 Schedule of Continued Access Procedures

Continued Access Schedule of Activities			
Visit[b]	**Study Treatment**	**Follow-Up[a]**	
Procedure			**Instructions**
AE Collection	X	X	Grading via CTCAE, Version 5.0. As part of AE collection, monitor vital signs and perform standard laboratory tests at the same frequency as during the study treatment period. All laboratory tests during the continued access period will be performed in the local laboratories only. Tumor evaluation will be performed per local standards.
Administer selpercatinib	X		Administer according to Section 5.2
Long-term safety for select patients	X	X	Height, weight, and Tanner staging (until patient reaches sexual maturity) every 12 weeks and date of menarche (for females, if occurs) for patients 12-17 and up to 5 years from treatment start date.

Abbreviations: AE = adverse event; CTCAE = common terminology criteria for adverse events (NCI 2018); NCI = National Cancer Institute.

a Continued-access follow-up begins when the participant and the investigator agree that the participant will no longer continue treatment in the continued access period and lasts approximately 30 days following the last dose of study drug. 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.

b Patient visits during continued access should continue at a minimum of every 84 ± 7 days for IP dispensing. Where allowed by local regulations, patients may alternate visits between the study site and remote visits with sponsor approval. Additional visits may be performed as clinically indicated.

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 or 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 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.

In exceptional circumstances, the flexibility measures outlined in the Schedule of Assessments (Table 11-1) and this appendix may be considered for Cycles 2 and higher visits after consultation with and prior approval by the Sponsor.

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 compliant with Good Clinical Practice, enabling participants to continue safely in the study and maintaining the integrity of the study.

Informed consent

Additional consent/assent from the participant will be obtained for the below items, as required by Ethical Review Boards and local regulations. Minor participants must be re-consented if they reach the age of majority during the course of study, in order to continue participating for

participation in remote visits, as defined in Section j ≥× ≥)n " "
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 how study conduct will be performed (e.g., virtual vs at the investigative site) will not be considered protocol deviations. Every effort should be made for the participant to return to on-site visits as soon as reasonably possible, while ensuring the safety of the participant and investigational site staff.

Remote visits

In source documents and the CRF, the study site should capture the method of visit (e.g., virtual, in-person), with a specific explanation for any data missing because of missed in-person site visits. Remote visits may include a combination of telemedicine, local physician assessments, or mobile healthcare as y "y ≥8yy•• ≤" –))–≥)" ≥ "–y)≤" • ≥ ")y ≤) " ≥)y y,,) by the Sponsor.

Assessments may be completed by a combination of video conference (telemedicine), local physician assessments, or mobile healthcare for Cycles 2 and higher visits.

Applicable assessments include physical examination and Karnofsky or Lansky, vital signs, patient PROs, and patient diaries. Other assessments, such as applicable blood draws for local labs, urinalysis, pregnancy tests, and 12-lead ECG (only for Cycles 7 and higher) may be completed remotely according to local regulations at a local clinic without video conference at –≥)" ≥ "–y)≤" • ≥ " :)a√) –≥≥")y)• •≥)≤ " –) –≥) ≥× ≥) " "8) –≥) y "•" y) — ,,≤) have an on-site follow-up visit as soon as possible.

Telemedicine: Telephone or technology-assisted virtual visits, or both, are acceptable to complete appropriate assessments.

Mobile healthcare: Healthcare visits may be performed at locations other than the study site (for example, y "•" y)—× ≥or at a local clinic) when participants cannot travel to the site due to an exceptional circumstance. Such visits will be performed by a mobile healthcare provider trained on the study.

Other alternative locations: Other procedures that may be done at an alternate location in exceptional circumstances

Safety reporting

Regardless of the type of remote visits implemented, the protocol requirements regarding the reporting of AEs, SAEs, and product complaints remain unchanged.

Return to on-site visits

Every effort should be made to enable participants to return to on-site visits as soon as reasonably possible, while ensuring the safety of both the participants and the site staff.

Study intervention and ancillary supplies (including participant diaries)

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

- asking the participant, parent, or guardian to go to the site and receive study supplies from site staff without completion of a full study visit
- asking the participant)designee to go to the site and receive study supplies on a y “• “ y)z≥–y,,√8)or
- 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 ≥ “√•y “) √) y “• “ y) ≥•≥“) √) ≤) „“≥ :
- When delivering supplies to a location other than the study site (for example, y “• “ y)—× ≥), the investigator or 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.

Screening period guidance

If the screening period lasts for more than 35 days due to exceptional circumstances, the participant must be discontinued because of screening interruption. This is documented as a screen fail in the CRF. The participant can reconsent and be rescreened as a new participant with a new participant number.

Any screening procedures that fall outside of the required windows per the JZJJ Protocol Schedule of Screening Activities (Protocol Section 7.2) must be repeated.

Adjustments to visit windows

Whenever possible and safe to do so, as determined by –≥)“ ≥ “–y)≤“ • ≥“ , participants should complete the usual Schedule of Activities. To maximize the possibility that these visits can be conducted as on-site visits, the windows for visits may be adjusted, upon further guidance from the Sponsor. This minimizes missing data and preserves the intended conduct of the study.

This table describes the allowed adjustments to visit windows.

Visit Number	Tolerance
Cycle 1 through Cycle 6, Safety Follow-Up, and Long-Term Follow-Up	No adjustment from windows described in Table 11-1.
Cycles 7 and higher	Window of timing may be extended to ±7 days.

For participants whose visits have extended windows, additional study intervention may need to be provided to avoid interruption and maintain overall integrity of the study.

Documentation

Changes to study conduct will be documented

Sites will identify and document the details of how participants, visit 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 “ ≥ “–y source documentation and should be transferred to the site in a secure and timely manner.

Appendix M Country-specific Requirements

This section describes protocol changes applicable for participants in study sites within Germany, France, UK, Canada, EU, and Japan.

The revised text in the following sections show the changes applicable for study participants within Germany, France, UK, Canada, EU, and Japan. Additions are identified by underline. Deletions are identified by ~~strikethrough~~ format.

EU:

Section 3.3 General Treatment Procedures

Patients with locally advanced disease with RECIST v1.1 confirmed response of CR/PR may [illegible] ~~These patients may undergo an optional tissue biopsy and/or additional imaging (e.g., PET/CT) at the time of consideration of treatment discontinuation. The purpose of these additional studies is to provide additional pathologic/radiographic information about disease status (e.g., presence or absence of tumor). Following treatment discontinuation, these patients will continue to be followed with radiologic assessment every 3 months for 2 years, and then every 6 months thereafter, using the same imaging modality(ies) as during treatment. An optional radiographic disease assessment may be performed 1 month after the interruption of selpercatinib at the discretion of the Investigator. If a [illegible] may re-start selpercatinib. At the time of selpercatinib re-initiation, the patient will start assessments per protocol as delineated for patients on active treatment. Patients who re-initiate selpercatinib treatment are permitted to have their selpercatinib treatment held again.~~

~~Patients who undergo surgical resection for local control may continue to receive selpercatinib after surgical recovery and discussion between the Investigator and the Sponsor. These patients should have selpercatinib held for 7 days prior to surgery and resumed 14 days after surgery. If the resection surgery results in negative margins and study drug is interrupted, disease assessments, as described in Section 7.13, should be performed every 3 months following the last dose of study drug. These patients are permitted to restart study drug if they experience PD after [illegible]~~

~~All treated patients will undergo a safety follow-up visit at 28 days (+7 days) after the last dose of study treatment and long-term follow-up visits at 3-month intervals (± 1 month) and until the study is officially closed.~~

Section 4.1 Inclusion Criteria

11. Adequate hepatic / pancreatic function, defined as:

    a.) Alanine aminotransferase (ALT) and aspartate aminotransferase [illegible] the upper limit of [illegible] ULN with documented liver involvement (such as liver metastasis or a primary biliary tumor)

    b.) [illegible] ULN with documented liver involvement [illegible] case may be enrolled with prior Sponsor approval), and

    c.) [illegible]

Section 7.11.3 Serum Chemistries

Serum chemistries (non-fasting) should be assessed in accordance with the Schedule of Assessments (Table 11-1) and should include assessment of the following: alkaline phosphatase, albumin, ALT, AST, BUN or urea, creatinine, glucose, LDH, total and direct bilirubin,

pancreatic lipase, total protein, phosphorus, sodium, potassium, chloride, calcium, magnesium, and bicarbonate.

Appendix A Study Assessments

[g] Serum chemistries (non-fasting) will include alkaline phosphatase, albumin, ALT, AST, BUN/urea, creatinine, glucose, LDH, total and direct bilirubin, pancreatic lipase, total protein, phosphorus, sodium, potassium, chloride, calcium, magnesium and bicarbonate.

Germany:

Implementation of this Appendix L

The changes to procedures described in ~~this appendix~~ Appendix L are temporary measures intended to be used only during specific time periods as directed by the Sponsor in partnership with the Investigator. In Germany, Appendix L is only applicable for exceptional circumstances related to COVID-19.

Spain:

Remote visits

Where allowed by local regulations, patients may alternate visits between the study site and remote visits with sponsor approval.

France:

Section 5.3.4.7 Substrates of BCRP and P-gp

Selpercatinib is an inhibitor of BCRP and P-gp. Substrates of BCRP and P-gp with narrow therapeutic index should be used with caution.

Table 11-1 Schedule of Assessments

[e] ECGs should be resting 12-lead ECG performed during Screening (in triplicate) and during Cycle 1 at the following time points: pre-dose (triplicate, ±10 minutes, up to 4 hours pre-dose), C1D1 ~~pre-dose and~~ at 2 ~~and 4~~ hours post-dose, (triplicate, ±10 minutes) and on C1D8 pre-dose and at 2 and 4 hours post-dose, (triplicate, ±10 minutes). ~~In addition, ECGs should be obtained pre-dose and 2 hours post-dose (±10 minutes) on C2D1 and pre-dose Cycles 3-EOT.~~ In addition, triplicate ECGs should be obtained 2 hours (± 10 minutes) post selpercatinib dosing on C2D1, C3D1, C4D1, C5D1, and C6D1. Thereafter, ECGs should be obtained (in triplicate) every 12 weeks at 2 hours (± 10 minutes) post selpercatinib dosing. Additional ECGs may be performed if clinically indicated. If 2 of the 3 ECGs demonstrate QTc 481-500 msec, perform additional ECG (in triplicate) at 4 hours (± 10 minutes) post dosing. If 2 of the 3 ECGs demonstrate QTc > 500 msec, repeat the ECG (triplicate) and manually review to confirm accuracy. If QTc > 500 msec is confirmed on 2/3 ECGs, hold selpercatinib and assess for alternative causes (concomitant medications, electrolyte abnormalities). Selpercatinib may be resumed at one reduced dose level when QTc has returned to baseline value, and with continued ECG monitoring as noted in the assessment schedule. ~~Additional ECGs may be performed if clinically indicated.~~ For intra-patient dose escalation, triplicate ECGs should be performed pre-dose (up to 4 hours pre-dose) and at 2 hours post-selpercatinib-dose (±10 minutes) on Day 1 ~~and 8~~ √) –≥) y ‘≥) ≥)≤ ≥8) and at ~~pre-dose~~, 2 ~~and 4~~ hours post-selpercatinib-dose (triplicate, ±10 minutes))Ty)H) √) –≥) y ‘≥) ≥)≤ ≥:)V) y ‘≥))AE) ≥y) ,,≤8)Ry ≥)V × ,,y) “,,,)z≥) “,“ ><))<> ≥ × “ ≥)i 1 •:)V) y ‘≥)N)AE) ≥y) ,,≤8)≥“ –≥)× ≥ —≤8)V ‘<> ‘•‘y))Ry ≥)V × ,,y)× y)z≥)y lied.

Remote visits

Where allowed by local regulations, patients may alternate visits between the study site and remote visits with sponsor approval.

UK:

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

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

Section # and Name	**Description of Change**	**Brief Rationale**
Synopsis	Dose limiting toxicity definition updated. Updated Inclusion Criterion 14 and exclusion criterion 6	Correction
Section 3.1.1.1. Dose-Limiting Toxicity Definition	Dose limiting toxicity definition updated.	Correction
Section 4.1. Inclusion Criteria	Contraception guidance in criterion 14 updated	Per country-specific amendment
Section 4.2. Exclusion Criteria	Criterion number 6 updated	Clarification
Section 5.3.2. Prior and Concomitant Medications	Information about selpercatinib substrate for CYP3A4 removed	Per country-specific amendment
Section 5.4. Duration of Treatment	Treatment duration with selpercatinib modified	Clarification
Section 7.1. Informed Consent/Pediatric Assent	Information about fertility preservation for patients and phototoxicity due to selpercatinib added	Per country-specific amendment
Study Assessments	Section number for Adverse events has been updated Specified in the last footnote that the screening pregnancy test must be a serum sample	For clarification Per country-specific amendment

SECTION PROTOCOL SYNOPSIS

STUDY DESIGN:

Dose-Limiting Toxicity Definition

Grade 3 uncomplicated febrile neutropenia lasting >48 hours is ~~*will not* be considered~~ a DLT

ELIGIBILITY CRITERIA:

Inclusion Criteria

14. Willingness of male and female patients with reproductive potential to utilize double effective birth control methods, defined as one used by the patient and another by his/her partner, for the duration of treatment and for ~~3~~ 1 month following study completion.

~~For m~~Male patients with a non-pregnant female partner of child-bearing potential or female patients of child-bearing potential with a male partner ~~and woman of child-bearing potential, one of the following highly effective birth control methods (with a failure rate of less than 1% per year when used consistently and correctly) are recommended~~ must agree to use contraception/barrier as detailed below:

Agree to use a male condom (if not vasectomized) AND

Agree to use of an additional highly effective birth control method with a failure rate <1% per year (such as combination oral contraceptives, implanted contraceptives, or intrauterine device, as listed below)

Highly effective birth control methods include:

a) Combined estrogen and progestogen containing hormonal contraception associated with inhibition of ovulation given orally, intravaginally, or transdermally

b) Progestin-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: considered a highly effective method only if defined as refraining from heterosexual intercourse during an entire period of risk associated with the study treatment. The reliability of sexual abstinence will be evaluated in relation to the duration of the study and to the usual lifestyle of the patient.

According to CTFG guidelines, the definition to of a female of child-bearing potential is as follows: a woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used

to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

Exclusion Criteria

6.Uncontrolled hypotension or hypertension ~~—~~>140/90 mm Hg ~~Grade 3 CTCAE (v5.0).~~

Section 3.1.1.3 Dose-Limiting Toxicity Definition

Grade 3 uncomplicated febrile neutropenia lasting >48 hours is ~~*will not* be considered~~ a DLT.

SECTION 4. SELECTION OF STUDY POPULATION

Section 4.1 Inclusion Criteria

14. Willingness of male and female patients with reproductive potential to utilize double effective birth control methods, defined as one used by the patient and another by his/her partner, for the duration of treatment and for ~~3~~ 1 months following study completion.

~~For m~~Male patients with a non-pregnant female partner of child-bearing potential, or female patients of child-bearing potential with a male partner ~~and woman of child-bearing potential, one of the following highly effective birth control methods (with a failure rate of less than 1% per year when used consistently and correctly) are recommended~~ must agree to use contraception/barrier as detailed below:

Agree to use a male condom (if not vasectomized) AND

Agree to use of an additional highly effective birth control method with a failure rate <1% per year (such as combination oral contraceptives, implanted contraceptives, or intrauterine device, as listed below)

Highly effective birth control methods include:

a) Combined estrogen and progestogen containing hormonal contraception associated with inhibition of ovulation given orally, intravaginally, or transdermally

b) Progestin-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: considered a highly effective method only if defined as refraining from heterosexual intercourse during an entire period of risk associated with the study treatment. The reliability of sexual abstinence will be evaluated in relation to the duration of the study and to the usual lifestyle of the patient.

According to CTFG guidelines, the definition to of a female of child-bearing potential is as follows: a woman is considered of childbearing potential (WOCBP), i.e. fertile, following

menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

Birth control methods *unacceptable* for this clinical trial are:

a) Periodic abstinence (calendar, sympto-thermal, or post-ovulation methods)

b) Withdrawal (coitus interruptus)

c) Spermicide only

d) Lactational amenorrhea method

Section 4.2 Exclusion Criteria

6. Uncontrolled hypotension or hypertension —>140/90 mm Hg. ~~Grade 3 CTCAE (v5.0).~~

Section 5.3 Prior and Concomitant Medications

Section 5.3.2 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 or thrombocytopenia in accordance with American Society for Clinical Oncology (ASCO) and/or European Society for Medical Oncology guidelines, transfusions, anti-emetics and anti-diarrheals, and glucocorticoids (up to 10 mg dexamethasone or 50 mg of prednisone or equivalent), including short courses to treat asthma, chronic obstructive pulmonary disease (COPD), or other systemic, chronic diseases that are normally treated with short courses of glucocorticoids. ~~As selpercatinib is a substrate of CYP3A4, patients should avoid inhibitors or ≤ •≥) √)Sq hCQD)"√) "z,,≥)y) ≥)• ,,≤)y,,≥) ≥)≤)hc :~~ Continuation of standard of care or supportive care medications that the patient has been on for the previous 28 days are allowed.

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

Coadministration of selpercatinib with sensitive CYP3A4 substrates may increase their plasma concentrations, which may increase the incidence or severity of adverse reactions for sensitive substrates with narrow therapeutic windows. If coadministration of a sensitive CYP3A4 substrate cannot be avoided, follow recommendations for modified dosing of these substrates in their approved product labeling and monitor for increased adverse reactions of these drugs.

Section 5.4 Duration of Treatment

It is anticipated that a patient on this study will receive treatment with open-label selpercatinib until the patient is able to obtain commercially available selpercatinib in their respective country, the patient does not meet criteria requiring discontinuation of treatment (refer to Section 6.1 Removal of Patients from Therapy or Assessment), and the y "≥) y "• " y ")" the study

has not ended:)m)• × × ≥ •‘y,,)y y‘‘;yz‘‘;‘‘)‘‘)≥y•—) y ‘‘≥) ≥ ≥• ‘‘ ≥)• 8) —≥ ≥)× y)z≥) additional options for the patient to continue to receive selpercatinib once the regulatory requirements are satisfied. These may include but are not limited to a rollover trial, patient assistance (should the patient qualify), or commercial selpercatinib. 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.

Section 7.1 Informed Consent/Pediatric Assent

Patients must be able to provide written informed consent (or pediatric assent, when applicable) and meet eligibility criteria prior to enrollment. Separate ICFs will be required for patients enrolling in Phase 1 and in Phase 2. Additional details are provided in Section 10.1.3.

Based on findings for potential toxicity from animal studies, patients should be counseled to consider fertility preservation prior to initiation of study treatment.

As no data are available on the potential for phototoxicity with use of selpercatinib, patients should be counseled to minimize exposure to UV light during treatment and for one month following the completion of treatment.

Study Assessments

Table 11-1 Schedule of Assessments(for UK only)

Evaluation	Screening	28-Day Cycles			End of Treatment (EOT)	Safety Follow-Up	Long-Term Follow-Up (LTFU)
		Cycle 1[q]	Cycles 2 through 12	Cycles 13 and Higher			
Visit Window	**(Day -28 to Day 0)**	**± 2 Days**	**± 3 Days**	**± 7 Days**	**± 3 Days**	**Day 28 +7 days**	**Every 3 months ± 1 month**
Informed Consent/Pediatric Assent	X	—	—	—	—	—	—
History of current malignancy	X	—	—	—	—	—	—
Urine or serum pregnancy test (if applicable)*	X	X	X	X	—	—	
Tissue biopsy [a]	X	—	—	—	X	—	—
Physical examination and Karnofsky or Lansky [b]	X	Days 1, 8, 15	Day 1	Day 1[v]	X	X	—
Vital signs [c]	X	Days 1, 8, 15, pre-dose	Day 1 pre-dose	Day 1 pre-dose[v]	X	X	—
CCI [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12-lead ECG [e]	X	Day 1, 8	Day 1	Day 1[v]	X	X	—
Hematology [f]	X	Days 1, 8, 15	Day 1	Day 1[v]	X	X	—

Approved on 21 Feb 2025 GMT

Evaluation	Screening	28-Day Cycles			End of Treatment (EOT)	Safety Follow-Up	Long-Term Follow-Up (LTFU)
		Cycle 1[q]	Cycles 2 through 12	Cycles 13 and Higher			
Visit Window	**(Day -28 to Day 0)**	**± 2 Days**	**± 3 Days**	**± 7 Days**	**± 3 Days**	**Day 28 +7 days**	**Every 3 months ± 1 month**
Serum chemistries [g]	X	Days 1, 8, 15	Day 1, Day 15 (Cycles 2-4) Day 1 (Cycles 5-12)	Day 1[v]	X	[X] [r]	
Urinalysis [h]	X	Day 1	Day 1	Day 1[u,v]	X	[X] [r]	
Thyroid Hormone (TSH and T4 or free T4 per local standard)	X		Day 1 of odd cycles beginning with C3	Day 1 of every 3rd cycle starting at Cycle 13[v]			
Patients with MTC OR OTHER THYROID CARCINOMA ONLY: TSH	X	Day 15	Day 1 of odd cycles beginning with C3	Day 1 of every 3rd cycle starting at Cycle 13			
Patients with MTC ONLY: Calcitonin, thyroglobulin, CEA	X	Day 1, 8, 15	Day 1	Day 1 of every 3rd cycle starting at Cycle 13	Day 1		Day 1
Patients with MTC (or other cancer patients [illegible]) cortisol, serum ACTH	X	Day 1	Day 1	Day 1 of every 3rd cycle starting at Cycle 13			

Evaluation	Screening	28-Day Cycles			End of Treatment (EOT)	Safety Follow-Up	Long-Term Follow-Up (LTFU)
		Cycle 1[q]	Cycles 2 through 12	Cycles 13 and Higher			
Visit Window	**(Day -28 to Day 0)**	**± 2 Days**	**± 3 Days**	**± 7 Days**	**± 3 Days**	**Day 28 +7 days**	**Every 3 months ± 1 month**
Growth plate evaluation [i]	X		q 6 months (if patent)	q 6 months (if patent)	q 6 months (if patent)	q 6 months (if patent)	q 6 months (if patent)
Dental evaluation [j]	X		q 6 months (if no full set of permanent teeth)	q 6 months (if no full set of permanent teeth)	q 6 months (if no full set of permanent teeth)	q 6 months (if no full set of permanent teeth)	q 6 months (if no full set of permanent teeth)
Pubertal maturation evaluation [k]	X		q 6 months until pubertal maturity	q 6 months until pubertal maturity	q 6 months until pubertal maturity	q 6 months until pubertal maturity	q 6 months until pubertal maturity
Menarche (female patients only)	Collect the date of menarche as medical history, if applicable	Collect the date of menarche if it occurs during the course of the study.					

Evaluation	Screening	28-Day Cycles			End of Treatment (EOT)	Safety Follow-Up	Long-Term Follow-Up (LTFU)
		Cycle 1[q]	Cycles 2 through 12	Cycles 13 and Higher			
Visit Window	**(Day -28 to Day 0)**	**± 2 Days**	**± 3 Days**	**± 7 Days**	**± 3 Days**	**Day 28 +7 days**	**Every 3 months ± 1 month**
Disease assessment[l]	X	—	Day 1 (±7 days) Cycle 2 (optional) and odd cycles	Day 1 (±7 days) every third cycle starting at Cycle 14	[X] [s]	—	X [t]
Telephone follow-up	—	Day 22	—	—	—	—	—
Pain CCI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Whole blood for CCI		Day 1, 15	Day 1 odd cycles to coincide with disease assessment	Day 1 every 12 cycles starting at Cycle 14 to coincide with disease assessment	X	—	—
Whole blood for genomic CCI	X	—	—	—	—	—	—
Selpercatinib administration	—	→	→	→	→	—	—
Patient dosing diary	—	→	→	→	→	—	—
Patient palatability questionnaire[x] (CCI)	—	—	As directed during alternate formulation assessment		—	—	—

Evaluation	Screening	28-Day Cycles			End of Treatment (EOT)	Safety Follow-Up	Long-Term Follow-Up (LTFU)
		Cycle 1[q]	Cycles 2 through 12	Cycles 13 and Higher			
Visit Window	(Day -28 to Day 0)	± 2 Days	± 3 Days	± 7 Days	± 3 Days	Day 28 +7 days	Every 3 months ± 1 month
Patient acceptability questionnaire[x] (CCI)	—	—	As directed during alternate formulation assessment		—	—	—
Adverse events [p]	→	→	→	→	→	→	—
Concomitant medications	→	→	→	→	→	→	—

Abbreviations for Table 11-1 and Footnotes: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; AUC_{0-24} = area under the curve time 0 to 24 hours; BUN = blood urea nitrogen; C1D1 = Cycle 1 Day 1; CEA = carcinoembryonic antigen; CCI CNS = central nervous system; CSF = cerebrospinal fluid; CT = computerized tomography; DLTs = dose-limiting toxicities; DNA = deoxyribonucleic acid; ECG = electrocardiogram; EOT = end of treatment; h = hour; CCI LDH = lactate dehydrogenase; LTFU = long-term follow-up; MIBG = meta-iodobenzylguanidine; MRI = magnetic resonance imaging; PedsQL-Core = Pediatrics Quality of Life - Core Module; PET = positron emission tomography; PK = pharmacokinetics; RBC = red blood cell; UPC = urine protein: creatinine ratio; WBC = white blood cell; SAE = serious adverse event.

Footnotes for Schedule of Assessments:

[a] Availability of tissue biopsy is required following the most recent progression. If tissue meeting this criterion is not available, a tissue sample obtained prior to most recent progression is acceptable. If neither of these samples are available for submission, then a fresh tumor biopsy is requested if it can be safely obtained. If no tissue is available the patient may still be eligible for enrollment following conversation with the Sponsor. Tissue biopsy collected at the EOT visit is optional. Additional biopsies may be requested on a case-by-case basis in patients re-starting study drug following a "drug holiday" and disease recurrence.

[b] Physical examination includes review of systems: breast/chest, extremities, genitourinary, head/ears/eyes/nose/throat, lymph nodes, musculoskeletal, pulmonary, and skin, thorough neurologic assessment, body weight, and height during Screening. Symptom-directed physical and neurological examinations, including measurement of weight and height, will be performed as part of vital signs. Karnofsky should be assessed for those 16 years old or older, or Lansky should be assessed for those younger than 16 years.

[c] **Vital signs on Day 1** should be predose. **Vital signs on Day 8** should be predose and at CCI **Vital signs on Day 15** should be Pre-dose. Vital signs in Cycles 2 and beyond should be predose.

[d] **Blood for PK** will be collected as outlined in Appendix B**.**

[e] ECGs should be resting 12-lead ECG performed during Screening and during Cycle 1 at the following time points: pre-dose (±10 minutes, up to 4 hours pre-dose), C1D1 pre-dose and 2 and 4 hours post-dose (±10 minutes), C1D8 pre-dose and 2 and 4 hours post-dose (±10 minutes). In addition, ECGs should be obtained pre-dose and 2 hours post-dose (±10 minutes) on C2D1 and pre-dose Cycles 3-EOT. Additional ECGs may be performed if clinically indicated. For intra-patient dose escalation, ECGs should be performed pre-dose (up to 4 hours pre-dose) on Day 1 and 8 of the patient's new dose, at pre-dose, 2 and 4 hours post-dose (±10 minutes).

[f] Hematology will include Hb, hematocrit, RBC count, WBC count with differential (neutrophils [absolute count and percent] and lymphocytes, monocytes, eosinophils, basophils [percent]), and platelet count.

[g] Serum chemistries (non-fasting) will include alkaline phosphatase, albumin, ALT, AST, BUN/urea, creatinine, glucose, LDH, total and direct bilirubin, total protein, phosphorus, sodium, potassium, chloride, calcium, magnesium and bicarbonate.

[h] If performed by dipstick, abnormal results should be followed by a complete urinalysis, including color, specific gravity, pH, glucose, bilirubin, ketones, occult blood, protein, leukocytes, nitrites and urobilinogen. If +2 protein is observed; a 24-hour urine collection or UPC ratio will be taken in order to quantify proteinuria.

[i] Patients who have not yet obtained full adult height will undergo imaging (anterior posterior and lateral views) of the right knee at baseline and every 6 months during participation in the study while the growth plate remains patent. If it is unclear that a patient has obtained full adult height, a pre-treatment tibial imaging (anterior posterior and lateral views) of the right knee should be obtained. If the growth plate remains patent, the patient will have an imaging (anterior posterior and lateral views) performed every 6 months during participation in the study until the growth plate is no longer patent.

[j] Patients aged 5 and older, without a full set of permanent teeth, will undergo a dental evaluation at baseline and every 6 months during participation in the study. Patients who enroll prior to their 5th birthday will start dental assessments at the cycle visit-closest to their 5th birthday. Changes in tooth development after baseline will be captured as an AE. Patients who enroll with a full set of permanent teeth will not need to undergo dental evaluations.

[k] Patients aged 7 and older will be assessed for pubertal maturation every 6 months during participation in the study based on the Tanner Scale. Patients who enroll prior to their 7th birthday will start assessment at the cycle visit closest to their 7th birthday. Delays to pubertal maturity (according to the Tanner Scale) after baseline will be captured as an AE. Patients who completed puberty according to the Tanner Scale at enrollment will not undergo evaluation.

[l] Tumor will be assessed by standard of care imaging modalities (CT and/or PET) or MRI of chest, abdomen, and pelvis, any other areas with suspected disease involvement. Patients enrolled with a history of CNS metastases should additionally have a head CT or MRI scan performed at each tumor assessment. Patients with locally advanced infantile fibrosarcoma should have an MRI or CT of the site of disease and a CT or X-Ray of the chest, plus any other areas of disease involvement. Patients with neuroblastoma will be followed with MIBG scans, anatomic imaging, and bilateral bone marrow aspirates and biopsies.

[m] CCI [redacted]

[n] Whole blood for CCI [redacted] should be obtained within 7 days following radiologic disease assessment, except for baseline/Screening when it may be obtained any time prior to treatment on C1D1. Whole blood for CCI [redacted] should be obtained at the EOT visit even if radiologic disease assessment is not performed. Patients less than 5 years of age will have 1×10 mL Streck tube drawn. Patients older than 5 years of age will have 2×10 mL Streck tube drawn. Sites may draw fewer tubes based on local institutional policy for maximal blood draws in patients.

[o] Whole blood for CCI [redacted] should be obtained any time during Screening prior to beginning treatment. Patients greater than 5 years of age will have one PAXGene tube (8.5 mL) drawn. Patients less than 5 years of age will not have any PAXGene tube drawn. Sites may draw fewer tubes based on local institutional policy for maximal blood draws in patients.

[p] Adverse event (AE) reporting should include the reporting of all AEs occurring for 28 days after the last dose of study drug regardless of cause of discontinuation. The reporting of SAEs should occur, according to SAE reporting criteria, until the patient discontinues the study or the study is closed. Refer to Section 8 ~~9~~ Adverse Events.

[q] During Cycle 1, observations will be performed prior to selpercatinib dosing on that day. Unless otherwise indicated, C1D1 evaluations may be performed either on Day -1 or predose on C1D1; if an evaluation is performed on Day -1, it need not be repeated on C1D1. Routine clinic visits performed within ± 2 days of the nominal visit day will not be considered protocol deviations.

[r] Repeat the assessment only if the EOT result showed treatment-emergent abnormalities.

[s] Assessment should be performed if no disease assessment was performed in last 2 cycles.

[t] Date of progression, as assessed by treating Investigator and survival status (may be conducted by phone). Refer to Section 7.19.

[u] Perform only as clinically indicated

[v] Perform every 12 weeks after 2 years on treatment.

[x] Questionnaires will be administered within approximately 30 minutes of dosing after the first dose of the CCI formulation and again after approximately 2 to 4 weeks of alternative formulation (CCI) administration and returned at the following clinic visit.

* Perform more frequently if required by local regulations. The screening pregnancy test must be a serum sample.

Canada:

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

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

Section # and Name	Description of Change	Brief Rationale
Protocol Synopsis	Table names specified for Table 3-1 Updated age of pediatric patients for Criterion 1, and pancreatic lipase statement added in Inclusion Criterion 11. Updated Table 2 in Criterion 12. Table and section number specified in Planned Sample Size. Sample Size Considerations phrase added in Statistical methods	Clarification As per country-specific amendment Clarification
Section 1.5.5 Clinical Experience	Section number specified for anticipated risks and Adverse Events.	Clarification
Section 3.3 General Treatment Procedures	Information about patients undergoing optional tissue biopsy and imaging removed Information about patients undergoing surgical resection removed	As per country-specific amendment
Section 4.1 Inclusion Criteria	Age modified for Criterion 1 X“;ƶ≥)≤“ ≥y ≥)y ≤) pancreatic lipase statement added in Criterion 11 Criterion 17 removed. Age and criteria updated in Table 4-1	As per country-specific amendment

Section 5.2.4.1 Management Guidelines for Specific Adverse Events	Information about adverse reactions to selpercatinib added	As per country-specific amendment
Section 7.7 Electrocardiograms	Information about more than one ECG tracing added	For clarification
Section 7.9 Dental Evaluation	Statement about patients enrolling before 5th birthday removed	As per country-specific amendment
Section 7.10 Pubertal Maturation Evaluation	Statement about patients enrolling before 7th birthday removed	As per country-specific amendment
Section 7.11.3 Serum Chemistries	Pancreatic lipase added	As per country-specific amendment
Section 9.3.1 Phase 1	Statement added about a maximum of 15 patients being enrolled onto dosing cohort	As per country-specific amendment
References	Reference for hepatotoxicity added	As per country-specific amendment
Study Assessments	Age criteria for patients undergoing dental evaluation, tanner scale assessment, and DNA updated	As per country-specific amendment

Section PROTOCOL SYNOPSIS

STUDY DESIGN:

Phase 1 Dose Escalation

If CCI patients within a cohort experience a DLT, then the dose escalation will stop. In order for the MTD/RP2D, the Safety Review Committee (SRC) will evaluate whether the previous lower dose level will be considered the MTD -(Synopsis Table 3-1 shows example doses), whether an intermediate dose level should be evaluated, and/or whether additional patients need to be evaluated if the DLTs seen at this dose level are considered to be not serious or equivocal with regard to causal relationship to selpercatinib.

Table 3-1 Planned Selpercatinib Dose Escalation Cohorts

Dose Level	Dose	Estimated Equivalent Adult Dose
-2	CCI	
-1		
1[a]		
2[a]		
3[a,b]		

Abbreviation: BID = twice daily.

[a] The Dose Levels listed, i.e., Dose Levels 1, 2, and 3, correspond to the Dose Cohorts 1, 2, and 3, respectively.

[b] Additional dose escalation may be considered based on the cumulative data (PK, safety, and efficacy) the actual dose determined by the SRC, not to exceed approximately 50% of the prior dose and taking into account capsule doses and capsule burden.

Phase 2 Expansion Cohorts

Additional patients may be enrolled to better characterize the safety and efficacy of the selpercatinib dose recommended for further study. Patients may enroll into each of the 4 cohorts below, depending on disease characteristics (refer to Synopsis Table 1).

Synopsis Table 1: Disease Criteria for Enrollment for Cohorts 1 to 4

Cohort	Disease Criteria
Cohort 1	RET fusion-positive solid tumor (excluding CNS primary) with measurable disease
Cohort 2	RET-mutant MTC with measurable disease
Cohort 3	RET fusion-positive primary CNS tumor with measurable disease
Cohort 4	Any patient with RET mutation/alteration not fitting Cohort 1 to 3 criteria (i.e., RET alterations via plasma cfDNA or non-CLIA certified test, non-measurable (i.e., only evaluable) disease

Abbreviations: cfDNA = circulating free DNA; CNS = central nervous system; MTC = medullary thyroid cancer.

ELIGIBILITY CRITERIA:

Inclusion Criteria

1. Pediatric patients ~~≥ ≥6 months~~ 2 years of age and ≤21 years of age at Cycle 1 Day 1 (C1D1) with a locally advanced or metastatic solid or primary CNS tumor that has relapsed, progressed or was nonresponsive to available therapies ~~and/or for which no standard or available systemic curative therapy exists~~.

11. Adequate hepatic / pancreatic function, defined as:

    a) Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2.5 × the upper limit of normal (ULN) or ≤5 × ULN with documented liver involvement (such as liver metastasis or a primary biliary tumor)

    b) Total bilirubin ≤1.5 × ULN or ≤3 × ULN with documented liver involvement or Gilbert's Disease (patients with Gilbert's Disease may be enrolled with prior Sponsor approval), *and*

c.) [illegible]

12. Adequate renal function, defined as:

a. Estimated glomeru[illegible] based on local institutional practice for determination, or a maximum serum creatinine by age and gender as presented in Synopsis Table 2.

Synopsis Table 2: Serum Creatinine by Age and Gender <u>for 2 years and above</u>

	Maximum Serum Creatinine (mg/dL)		**Maximum Serum Creatinine (µmol/L)**	
Age	**Male**	**Female**	**Male**	**Female**
~~**6 months to < 1 year**~~	~~**0.5**~~	~~**0.5**~~	~~**44**~~	~~**44**~~
~~**1 to < 2 years**~~	~~**0.6**~~	~~**0.6**~~	~~**53**~~	~~**53**~~
2 to <6 years	0.8	0.8	71	71
6 to <10 years	1	1	88	88
10 to <13 years	1.2	1.2	106	106
13 to <16 years	1.5	1.4	132	124
[illegible]	1.7	1.4	150	124

~~17. removed~~

PLANNED SAMPLE SIZE:

In the Phase 2 portion of the study, additional patients may be enrolled to better characterize the safety and efficacy of the selpercatinib RP2D. The Phase 2 portion will enroll approximately 10 to 20 patients into Cohorts 1 and 2 <u>(refer to Table 3-2 and Section 9.3)</u>. The total sample size for Phase 2 will not exceed 60 patients.

Table 3-2 Disease Criteria for Enrollment: Cohorts 1 to 4

Cohort	**Disease Criteria**
Cohort 1	RET fusion-positive solid tumor (excluding CNS primary) with measurable disease
Cohort 2	RET-mutant MTC with measurable disease
Cohort 3	RET fusion-positive primary CNS tumor with measurable disease

Cohort 4	Any patient with RET mutation/alteration not fitting Cohort 1 to 3 criteria (i.e., RET alterations via plasma cfDNA or non-CLIA certified test, measurable or non-measurable disease)

Abbreviations: cfDNA = circulating free DNA; CNS = central nervous system; MTC = medullary thyroid cancer.

STATISTICAL METHODS:

Sample Size Considerations:

1.5.5 Clinical Experience

Please refer to ~~for the most current~~ the selpercatinib IB for a summary of clinical experience, including anticipated risks and dose modification plans for specific AEs.

3 INVESTIGATIONAL PLAN

3.1.1 Study Design

Increase or decrease in dose level if indicated, will follow the Table 3-1 dose levels listed, to the next ~~appropriate~~ lower dose.

3.1.1.2 Dose Escalation Scheme and Assessment of Dose-Limiting Toxicity

No more than 15 patients will be enrolled into a Dose Escalation cohort.

3.3 General Treatment Procedures

Patients with locally advanced disease with RECIST v1.1 confirmed response of CR/PR may [illegible] discussion with the Spo[illegible]e :)~~These patients may undergo an optional tissue biopsy and/or additional imaging (e.g., PET/CT) at the time of consideration of treatment discontinuation. The purpose of these additional studies is to provide additional pathologic/radiographic information about disease status (e.g., presence or absence of tumor). Following treatment discontinuation, these patients will continue to be followed with radiologic assessment every 3 months for 2 years, and then every 6 months thereafter, using the same imaging modality(ies) as during treatment. An optional radiographic disease assessment may be performed 1 month after the interruption of selpercatinib at the discretion of the Investigator. If a [illegible] o have evidence of radiographic PD, the patient may re-start selpercatinib. At the time of selpercatinib re-initiation, the patient will start assessments per protocol as delineated for patients on active treatment. Patients who re-initiate selpercatinib treatment are permitted to have their selpercatinib treatment held again.~~ Additional information is outlined in Section 3.1.1.1.

~~Patients who undergo surgical resection for local control may continue to receive selpercatinib after surgical recovery and discussion between the Investigator and the Sponsor. These patients should have selpercatinib held for 7 days prior to surgery and resumed 14 days after surgery. If the resection surgery results in negative margins and study drug is interrupted, disease assessments, as described in Section 7.13, should be performed every 3 months following the last~~

~~dose of study drug. These patients are permitted to restart study drug if they experience PD after ≤“ • “) “) ≥)k)× ≥<“•y,,)× “ :~~

~~All treated patients will undergo a safety follow-up visit at 28 days (+7 days) after the last dose of study treatment and long-term follow-up visits at 3-month intervals (± 1 month) and until the study is officially closed.~~

4.1 Inclusion Criteria

~~1.~~ Pediatric patients ~~6 months~~ 2 years of age and 21 years of age at Cycle 1 Day 1 (C1D1) with a locally advanced or metastatic solid or primary CNS tumor that has relapsed, progressed or was nonresponsive to available therapies ~~and for which no standard or available systemic curative therapy exists~~.

a) Patients with locally advanced disease who would require, in the opinion of the Investigator, disfiguring surgery or limb amputation to achieve a complete surgical resection, are also eligible.
b) In geographies where a selective RET-inhibitor is approved, patients may enroll without prior systemic treatment.

11. Adequate hepatic / pancreatic function, defined as:

a) Q,,y “ ≥)y× “ y √≤ y ≥)4Qd1 5)y ≤)y y y ≥)y× “ y √≤ y ≥)4Qk1 5) B:E)× the ≥),,“× “) √) × y,,)4mdf 5)) E)× ULN with documented liver involvement (such as liver metastasis or a primary biliary tumor)

b) 1 y,,)z“,,“ z“) A:E)× mdf)) C)× ULN with documented liver involvement or X“,z≥)≤“ ≥y ≥4 y “≥) “—)X“,z≥)T“ ≥y ≥)× y)z≥)≥ ,,≥≤) “—) “)k) approval), *and*

c) hy • ≥y “•),,“ y ≥) A:E))mdf)4)k)y y,,5:

Table 4-1 Serum Creatinine by Age and Gender for age 2 and above

	Maximum Serum Creatinine (mg/dL)		Maximum Serum Creatinine (µmol/L)	
Age	**Male**	**Female**	**Male**	**Female**
~~**6 months to < 1 year**~~	~~**0.5**~~	~~**0.5**~~	~~**44**~~	~~**44**~~
~~**1 to < 2 years**~~	~~**0.6**~~	~~**0.6**~~	~~**53**~~	~~**53**~~
2 to <6 years	**0.8**	**0.8**	**71**	**71**
6 to <10 years	**1**	**1**	**88**	**88**
10 to <13 years	**1.2**	**1.2**	**106**	**106**
13 to <16 years	**1.5**	**1.4**	**132**	**124**

f ml	**1.7**	**1.4**	**150**	**124**

5.2.4.1 Management Guidelines for Specific Adverse Events

Hypersensitivity Reactions to Selpercatinib

Drug hypersensitivity reactions to selpercatinib have been reported. Rare patients developed a constellation of symptoms and findings characterized by a maculopapular rash, often preceded z)√≥ ≥ 8) "—)y •'y ≍)y —y,,–'y))× y,,–'y)≤ " –) –≥) y '≥)" "'y,,) ≥≥') √) ≥y × ≥ 8) 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) should be initiated. Upon resolution, selpercatinib may be resumed at a reduced dose of 40 mg (23 mg/m^2) 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 (46 mg/m^2) BID, 120 mg (70 mg/m^2) BID, and 160 mg (92 mg/m^2) 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 (23 mg/m2) BID, selpercatinib should be discontinued.

To understand further the mechanism of this AE, the Sponsor recommends assessment of serum IL-6, tumor data currently available, it may be appropriate to limit such testing to IL-6, which necrosis factor, and immunoglobulin E levels with each occurrence of hypersensitivity, at 3 hours after initial drug re-exposure, and at 3 hours after each dose escalation. Based on the limited may be used as a measure of reaction severity and increasing tolerance with re-exposure.

Liver Function Test Abnormalities with Selpercatinib

LFT laboratory testing (AST, ALT, total bilirubin, and ALP) should be performed every 2 weeks — —)SDTA)y ≤) –≥)TA) √)≥ ≥) z ≥ ≥) ≥y × ≥)• •,≥:)a√)y) y '≥)≥ ≥'≥ •≥) X y≤≥) 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, and 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 permitted with prior Sponsor approval). 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. Patients previously treated with ICIs remain eligible for the study.

Upon resolution, selpercatinib may be resumed at a reduced dose of 80 mg (46 mg/m^2) BID with weekly LFT monitoring. In the absence of recurrent LFT abnormalities, the dose of selpercatinib may be escalated sequentially to 120 mg (70 mg/m2) BID after a minimum of 2 weeks at 80 mg (46 mg/m^2) BID, and again to 160 mg (92 mg/m2) BID, and after a minimum of 4 weeks at 120 mg (70 mg/m^2) BID. Once the patient has been treated at a stable dose of selpercatinib for a minimum of 4 weeks without recurrent LFT abnormalities, the frequency of LFT monitoring may be decreased (e.g., every 2 weeks for 2 months and then monthly thereafter). For patients —)≥ ≥ “≥ •≥) X y<>)C)≥,≥ y ≍)d Vl)y)≤“√≥ ≥)≤ ≥) –y)AF>)× –)4l B)mg/m^2) BID, the Sponsor should be contacted for additional guidance regarding dose modification. If the patient ≥ ≥ “≥ •≥) X y<>)C)≥,≥ y ≍)d Vl)y)y)≤ ≥) √)D>)× –)4BC)× –« ^{2}) BID, selpercatinib should be discontinued.

Thrombocytopenia with Selpercatinib

A complete blood count (CBC) should be performed during Screening, C1D1, C1D15, and Day A) √)≥ ≥) z ≥ ≥)• •,≥:)a√)y) y “≥)“)≤“ • ≥≍)) –y ≥) — × z • ≥ “y) X y<>)C8) ≤) 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 [70 mg/m^2] BID or 80 mg [46 mg/m^2] BID) with weekly CBC surveillance for 1 full cycle. The Sponsor should be notified for consideration of concomitant steroid therapy and for further dose re-escalation.

Hypertension with Selpercatinib

Q,,,)“ ≥ “–y) — ,,≤)• “≤>) “× “ “ –) y “≥)z,, ≤) ≥ ≥))y)“≤>y,,) ≥y≤“ –) √) AD><I >)× × Y–)4“√) ≥•≥ y 5) “))“ “‘y “) √) ≤)≤ –:)a√)—pertension, defined as a y“ ≍)“ • ≥y ≥)“)z,, ≤) ≥ ≥)√ ×)zy ≥,“ ≥)) B) ≥y≤“ –)) B) ≥ y y ≥) ••y “ 8))y) 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, “≤>y,,,))y) ≥ ≤ •“z,,≥) ≥y≤“ –) √) AD><I >)× × Y–:)a√) ≤)≤ –)“)“ ≥ ≥≍8)“)× y)z≥) resumed at the same or a lower dose at the discretion of the Investigator. In all cases, the patient should continue to undergo regular blood pressure monitoring to ensure adequate blood pressure • ,,;)a√)–≥) y “≥)≥ ≥ “≥ •≥) • ,,≍) X y<>)C)— ≥ ≥ “)≤espite anti-hypertensive

regimen optimization and study drug dose reduction to 40 mg (23 mg/m2) BID, selpercatinib should be discontinued.

QTcF Prolongation with Selpercatinib

Q,,,) y "≥) — ,≤) y ≥)y)i 1 • V)" ≥ y,,) √) DG>)× ≥•) "))" "'y " –) –≥ y y with selpercatinib. If more than 1 ECG tracing is captured at any given time point during screening or on study, an average of the QTcF values should be used. Concomitant medications known to prolong the QTc interval should be avoided. ECGs should be collected and monitored, as indicated in the protocol, during Cycle 1 on Days 1 and 8, then monthly through Cycle 6 and every 12 weeks thereafter. During this time, electrolytes should be monitored and repletion ≥ • "z≍)y) ≥≍≍≤)4 y " ×) — ,≤)z≥) D)× Uq/L and <ULN and magnesium and calcium should be within normal limits).

Pleural Effusions and Abdominal Ascites with Selpercatinib

If a patient develops a pleural effusion and/or abdominal ascites 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 rare patients receiving selpercatinib have been reported to have effusions and/ or ascites which have subsequently been found to be chylous in nature. Distinguishing chylous fluid from malignant (as well as other causes such as infectious) may impact management significantly (e.g., presumption of disease progression with premature discontinuation of therapy). Additionally, a diagnosis of chylous effusions and/or ascites may reveal a role for conservative measures, such as fluid replacement, dietary alteration, and/or a trial of medical therapy (e.g., somatostatin analogue) prior to consideration of more invasive measures. Selpercatinib interruption and dose modification should follow the general strategy as outlined in study-specific protocols based upon severity and causality of the event.

7.7 Electrocardiograms

If more than one ECG tracing is captured at any given time point during screening or on study, an average of the QTcF or QTcB (as applicable) values should be used. Concomitant medications known to prolong the QTc interval should be avoided. ECGs should be collected and monitored during Cycle 1 on Days 1 and 8 and then monthly through Cycle 6 and every 12 weeks thereafter. During this time, electrolytes should be monitored and repletion prescribed as needed (potassium should be 4.0 mEq/L and <ULN, and magnesium and calcium should be within normal limits).

7.9 Dental Evaluation

Patients aged 5 years and older, without a full set of permanent teeth, will undergo a dental evaluation at baseline and every 6 months during participation in the study. ~~Patients who enroll prior to their 5th birthday will start dental assessments at the cycle visit closest to their 5th birthday.~~ Detrimental changes in tooth development considered significant after study baseline will be captured as an AE, and will require dentist evaluation.

7.10 Pubertal Maturation Evaluation

Patients aged 7 years and older will be assessed for pubertal maturation every 6 months during participation in the study based on the Tanner Scale. ~~Patients who enroll prior to their 7th birthday will start assessment at the cycle visit closest to their 7th birthday.~~ Delays to pubertal maturity (according to the Tanner Scale) after study baseline will be captured as an AE.

7.11.3 Serum Chemistries

Serum chemistries (non-fasting) should be assessed in accordance with the Schedule of Assessments (Table 11-1) and should include assessment of the following: alkaline phosphatase, albumin, ALT, AST, BUN or urea, creatinine, glucose, LDH, total and direct bilirubin, pancreatic lipase, total protein, phosphorus, sodium, potassium, chloride, calcium, magnesium, and bicarbonate.

9.3 Determination of Sample Size

9.3.1 Phase 1

If an investigative site identifies a patient with a known RET alteration, the patient may be ≥ „„≍))y) ≥ “)• —) –y) –y)z≥≥)≤≥ ≥ × “ ≍) y√≥)y√≥)≤“ • “) “ –) –≥)k) Medical Monitor. If a patient with a RET alteration is identified after 6 patients have been enrolled on Dosing Cohort 1, and prior to clearance of the DLT window, that patient will be enrolled to Dose Level -1. Following clearance of Dose Level 1, the patient(s) enrolled to Dose Level -1 may be escalated to Dose Level 1 upon discussion between the Investigator and the k)e ≍“•y„)e “ :)hy “≥) —)× “)G))× ≥)≤y) √)≤ “ –)“)S •„≥)A)√) ≥y) unrelated to study drug toxicity will be considered to have inadequate study drug exposure to support dose escalation and will be replaced. A maximum of 15 patients will be enrolled into a dosing cohort.

11. REFERENCES

Lin, J.J., Chin, E., Yeap, B.Y., Ferris, L.A., Kamesan, V., Lennes, I.T., Sequist, L.V., Heist, R.S., Mino-Kenudson, M., Gainor, J.F., Shaw, A.T. (2015) a • ≥y ≍)hepatotoxicity associated with sequential immune checkpoint inhibitor and crizotinib therapy in patients with non-small cell lung cy •≥ :)b)l — y•)g • „)AD4A5JACE-140.

Study Assessments

Table 11-1 Schedule of Assessments (for Canada only)

Evaluation	Screening	28-Day Cycles			End of Treatment (EOT)	Safety Follow-Up	Long- Term Follow-Up (LTFU)
		Cycle 1[q]	Cycles 2 through 12	Cycles 13 and Higher			
Visit Window	**(Day -28 to Day 0)**	**± 2 Days**	**± 3 Days**	**± 7 Days**	**± 3 Days**	**Day 28 +7 days**	**Every 3 months ± 1 month**
Informed Consent/Pediatric Assent	X	—	—	—	—	—	—
History of current malignancy	X	—	—	—	—	—	—
Urine or serum pregnancy test (if applicable)*	X	X	X	X	—	—	
Tissue biopsy [a]	X	—	—	—	X	—	—
Physical examination and Karnofsky or Lansky [b]	X	Days 1, 8, 15	Day 1	Day 1[v]	X	X	—
Vital signs [c]	X	Days 1, 8, 15, pre-dose	Day 1 pre-dose	Day 1 pre-dose[v]	X	X	—
CCI [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12-lead ECG [e]	X	Day 1, 8	Day 1	Day 1[v]	X	X	—
Hematology [f]	X	Days 1, 8, 15	Day 1	Day 1[v]	X	X	—
Serum chemistries [g]	X	Days 1, 8, 15	Day 1, Day 15 (Cycles 2-4) Day 1 (Cycles 5-12)	Day 1[v]	X	[X] [r]	—
Pancreatic lipase	X	Day 1	Day 1 (Cycles 2-12)	Every 3rd cycle starting at Cycle 13[v]	X		
Urinalysis [h]	X	Day 1	Day 1	Day 1[u,v]	X	[X] [r]	—
Thyroid Hormone (TSH and T4 or free T4 per local standard)	X		Day 1 of odd cycles beginning with C3	Day 1 of every 3rd cycle starting at Cycle 13[v]			

Evaluation	Screening	28-Day Cycles			End of Treatment (EOT)	Safety Follow-Up	Long- Term Follow-Up (LTFU)
		Cycle 1[q]	Cycles 2 through 12	Cycles 13 and Higher			
Visit Window	**(Day -28 to Day 0)**	**± 2 Days**	**± 3 Days**	**± 7 Days**	**± 3 Days**	**Day 28 +7 days**	**Every 3 months ± 1 month**
Patients with MTC OR OTHER THYROID CARCINOMA ONLY: TSH	X	Day 15	Day 1 of odd cycles beginning with C3	Day 1 of every 3rd cycle starting at Cycle 13			
Patients with MTC ONLY: Calcitonin, thyroglobulin, CEA[v]	X	Day 1, 8, 15	Day 1	Day 1 of every 3rd cycle starting at Cycle 13	Day 1		Day 1
Patients with MTC (or other cancer y “≥) “–)S —“ –)≤“ ≥y ≥5D)k≥ ×) cortisol, serum ACTH[v]	X	Day 1	Day 1	Day 1 of every 3rd cycle starting at Cycle 13			
Growth plate evaluation [i]	X		q 6 months (if patent)	q 6 months (if patent)	q 6 months (if patent)	q 6 months (if patent)	q 6 months (if patent)
Dental evaluation [j]	X		q 6 months (if no full set of permanent teeth)	q 6 months (if no full set of permanent teeth)	q 6 months (if no full set of permanent teeth)	q 6 months (if no full set of permanent teeth)	q 6 months (if no full set of permanen t teeth)
Pubertal maturation evaluation [k]	X		q 6 months until pubertal maturity	q 6 months until pubertal maturity	q 6 months until pubertal maturity	q 6 months until pubertal maturity	q 6 months until pubertal maturity
Menarche (female patients only)	Collect the date of menarche as medical	Collect the date of menarche if it occurs during the course of the study.					

Evaluation	Screening	28-Day Cycles			End of Treatment (EOT)	Safety Follow-Up	Long- Term Follow-Up (LTFU)
		Cycle 1[q]	Cycles 2 through 12	Cycles 13 and Higher			
Visit Window	**(Day -28 to Day 0)**	**± 2 Days**	**± 3 Days**	**± 7 Days**	**± 3 Days**	**Day 28 +7 days**	**Every 3 months ± 1 month**
	history, if applicable						
Disease assessment[l]	X	—	Day 1 (±7 days) Cycle 2 (optional) and odd cycles	Day 1 (±7 days) every third cycle starting at Cycle 14	[X] [s]	—	X [t]
Telephone follow-up	—	Day 22	—	—	—	—	—
Pain CCI							
Whole blood for CCI		Day 1, 15	Day 1 odd cycles to coincide with disease assessment	Day 1 every 12 cycles starting at Cycle 14 to coincide with disease assessment	X	—	—
Whole blood for CCI	X	—	—	—	—	—	—
Selpercatinib administration	—	→	→	→	→	—	—
Patient dosing diary	—	→	→	→	→	—	—
Patient palatability questionnaire[x] (CCI)	—	—	As directed during alternate formulation assessment		—	—	—
Patient acceptability questionnaire[x] (CCI)	—	—	As directed during alternate formulation assessment		—	—	—
Adverse events [p]	→	→	→	→	→	→	—
Concomitant medications	→	→	→	→	→	→	—

Abbreviations for Table 11-1 and Footnotes: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; AUC_{0-24} = area under the curve time 0 to 24 hours; BUN = blood urea nitrogen; C1D1 = Cycle 1 Day 1; CEA = carcinoembryonic antigen; CCI
CNS = central nervous system; CSF = cerebrospinal fluid; CT = computerized tomography; DLTs = dose-limiting toxicities; DNA = deoxyribonucleic acid;

ECG = electrocardiogram; EOT = end of treatment; h = hour; CCI [redacted] LDH = lactate dehydrogenase; LTFU = long-term follow-up; MIBG = meta-iodobenzylguanidine; MRI = magnetic resonance imaging; PedsQL-Core = Pediatrics Quality of Life - Core Module; PET = positron emission tomography; PK = pharmacokinetics; RBC = red blood cell; UPC = urine protein: creatinine ratio; WBC = white blood cell; SAE = serious adverse event.

Footnotes for Schedule of Assessments:

[a] Availability of tissue biopsy is required following the most recent progression. If tissue meeting this criterion is not available, a tissue sample obtained prior to most recent progression is acceptable. If neither of these samples are available for submission, then a fresh tumor biopsy is requested if it can be safely obtained. If no tissue is available the patient may still be eligible for enrollment following conversation with the Sponsor. Tissue biopsy collected at the EOT visit is optional. Additional biopsies may be requested on a case-by-case basis in patients re-starting study drug following a "drug holiday" and disease recurrence.

[b] Physical examination includes review of systems: breast/chest, extremities, genitourinary, head/ears/eyes/nose/throat, lymph nodes, musculoskeletal, pulmonary, and skin, thorough neurologic assessment, body weight, and height during Screening. Symptom-directed physical and neurological examinations, including measurement of weight and height, will be performed as part of vital signs. Karnofsky should be assessed for those 16 years old or older, or Lansky should be assessed for those younger than 16 years.

[c] **Vital signs on Day 1** should be predose. **Vital signs on Day 8** should be predose and at CCI [redacted] **Vital signs on Day 15** should be Pre-dose. Vital signs in Cycles 2 and beyond should be predose.

[d] **Blood for PK** will be collected as outlined in Appendix B**.**

[e] ECGs should be resting 12-lead ECG performed during Screening and during Cycle 1 at the following time points: pre-dose (±10 minutes, up to 4 hours pre-dose), C1D1 pre-dose and at 2 ~~and 4~~hours post-dose ~~(±10 minutes)~~ , C1D8 at 2 hours post-dose, ±10 minutes. On C2D1 ~~through C6D1 visits,~~ perform ECG at 2 hours (± 10 minutes) post selpercatinib dosing. ~~Thereafter,~~ From Cycle 3 through Cycle 6 ~~and beyond~~ , ECGs should be obtained pre-dose. From Cycle 6 and beyond, ECGs should be obtained pre-dose every 12 weeks. ~~and every 12 weeks at 2 hours post-dose (±(± 10 minutes) on C2D1 and pre-dose Cycles 3 EOT. Post selpercatinib dosing~~ During this time, electrolytes should be monitored and repletion prescribed as needed (potassium should be ≥4 mEq/L and <ULN, and magnesium and calcium should be within normal limits). Additional ECGs may be performed if clinically indicated. If any ECG demonstrates QTc 481-500 msec, perform an additional ECG at 4 hours (± 10 minutes) post dosing. If any ECG demonstrates QTc > 500 msec, repeat the ECG twice (triplicate in total) and manually review to confirm accuracy. If QTc > 500 msec is confirmed on 2/3 ECGs, hold selpercatinib and assess for alternative causes (concomitant medications, electrolyte abnormalities). LOXO-292 may be resumed at one reduced dose level when QTc has returned to baseline value, and with continued ECG monitoring as noted in the assessment schedule. For intra-patient dose escalation, ECGs should be performed predose (up to 4 hours pre-dose) 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 ≤15 years old, Bazett's Formula will be utilized to determine QTc. For patients >15 years old, either method, Fridericia or Bazett's Formula, may be applied.

[f] Hematology will include Hb, hematocrit, RBC count, WBC count with differential (neutrophils [absolute count and percent] and lymphocytes, monocytes, eosinophils, basophils [percent]), and platelet count.

[g] Serum chemistries (non-fasting) will include alkaline phosphatase, albumin, ALT, AST, BUN/urea, creatinine, glucose, LDH, total and direct bilirubin, total protein, phosphorus, sodium, potassium, chloride, calcium, magnesium, and bicarbonate.

[h] If performed by dipstick, abnormal results should be followed by a complete urinalysis, including color, specific gravity, pH, glucose, bilirubin, ketones, occult blood, protein, leukocytes, nitrites, and urobilinogen. If +2 protein is observed; a 24-hour urine collection or UPC ratio will be taken in order to quantify proteinuria.

[i] Patients who have not yet obtained full adult height will undergo imaging (anterior posterior and lateral views) of the right knee at baseline and every 6 months during participation in the study while the growth plate remains patent. If it is unclear that a patient has obtained full adult height, a pre-treatment tibial imaging

(anterior posterior and lateral views) of the right knee should be obtained. If the growth plate remains patent, the patient will have an imaging (anterior posterior and lateral views) performed every 6 months during participation in the study until the growth plate is no longer patent.

[j] Patients aged 5 and older, without a full set of permanent teeth, will undergo a dental evaluation at baseline and every 6 months during participation in the study. ~~Patients who enroll prior to their 5th birthday will start dental assessments at the cycle visit closest to their 5th birthday.~~ Changes in tooth development after baseline will be captured as an AE. Patients who enroll with a full set of permanent teeth will not need to undergo dental evaluations.

[k] Patients aged 7 and older will be assessed for pubertal maturation every 6 months during participation in the study based on the Tanner Scale. ~~Patients who enroll prior to their 7th birthday will start assessment at the cycle visit closest to their 7th birthday.~~ Delays to pubertal maturity (according to the Tanner Scale) after baseline will be captured as an AE. Patients who completed puberty according to the Tanner Scale at enrollment will not undergo evaluation.

[l] Tumor will be assessed by standard of care imaging modalities (CT and/or PET) or MRI of chest, abdomen, and pelvis, any other areas with suspected disease involvement. Patients enrolled with a history of CNS metastases should additionally have a head CT or MRI scan performed at each tumor assessment. Patients with locally advanced infantile fibrosarcoma should have an MRI or CT of the site of disease and a CT or X-Ray of the chest, plus any other areas of disease involvement. Patients with neuroblastoma will be followed with MIBG scans, anatomic imaging, and bilateral bone marrow aspirates and biopsies.

[m] Pain and HRQoL assessments will be collected every cycle. In patients 3 years of age or older, pain will be assessed by the Wong-Baker Faces Scale. For all patients HRQoL will be assessed using the PedsQL-Core for the patient or their parent/caregiver.

[n] Whole blood for CCI should be obtained within 7 days following radiologic disease assessment, except for baseline/Screening when it may be obtained any time prior to treatment on C1D1. Whole blood for CCI should be obtained at the EOT visit even if radiologic disease assessment is not performed. Patients less than 5 years of age will have 1×10 mL Streck tube drawn. Patients older than 5 years of age or older will have 2×10 mL Streck tube drawn. Sites may draw fewer tubes based on local institutional policy for maximal blood draws in patients.

[o] Whole blood for CCI should be obtained any time during Screening prior to beginning treatment. Patients less than 5 years of age will not have this sample drawn. Patients 5 years of age or older will have one PAXGene tube (8.5 mL) drawn. ~~Patients less than 5 years of age will not have any PAXGene tube drawn.~~ Sites may draw fewer tubes based on local institutional policy for maximal blood draws in patients.

[p] Adverse event (AE) reporting should include the reporting of all AEs occurring for 28 days after the last dose of study drug regardless of cause of discontinuation. The reporting of SAEs should occur, according to SAE reporting criteria, until the patient discontinues the study or the study is closed. Refer to Section 8 Adverse Events.

[q] During Cycle 1, observations will be performed prior to selpercatinib dosing on that day. Unless otherwise indicated, C1D1 evaluations may be performed either on Day -1 or predose on C1D1; if an evaluation is performed on Day -1, it need not be repeated on C1D1. Routine clinic visits performed within ± 2 days of the nominal visit day will not be considered protocol deviations.

[r] Repeat the assessment only if the EOT result showed treatment-emergent abnormalities.

[s] Assessment should be performed if no disease assessment was performed in last 2 cycles.

[t] Date of progression, as assessed by treating Investigator and survival status (may be conducted by phone). Refer to Section 7.19.

[u] Perform only as clinically indicated

[v] Perform at least every 12 weeks after 2 years on treatment. Align with disease assessment visits.

[x] Questionnaires will be administered within approximately 30 minutes of dosing after the first dose of the CCI formulation and again after approximately 2 to 4 weeks of alternative formulation (CCI) administration and returned at the following clinic visit.

[*] ~~Perform every 12 weeks after 2 years on treatment~~ Perform more frequently if required by local regulations.

Japan:

This section describes protocol changes applicable for participants in study sites in Japan

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

Section # and Name	Description of Change	Brief Rationale
Section Synopsis	Information about selpercatinib administration as capsule or liquid suspension added. Information about subject hospitalization and not enrolled in phase 1 dose escalation removed Information about Japan participants added	As per regulatory requirement
Section 3.2 Phase 2 Dose Expansion Cohort	Information about subject hospitalization and not enrolled in phase 1 dose escalation removed Information about Japan participants added	As per regulatory requirement
Section 4.1 Inclusion Criteria	Information mentioned about contraception methods not applicable in Japan	As per regulatory requirement
Study Assessments	Information about subject hospitalization and not enrolled in phase 1 dose escalation removed Information about Japan participants added	As per regulatory requirement

Section Synopsis

STUDY DESIGN:

Phase 2 Expansion Cohorts

Selpercatinib is administered in oral capsule or liquid suspension. Each cycle consists of 28 days.

JAPAN ONLY:

~~**Subjects in Japan will be hospitalized during Cycle 1 in Phase 1.**~~

~~**If a subject in Japan has not been enrolled in Phase 1 Dose Escalation, at least 1 subject in Phase 2 is required to be monitored by hospitalization during Cycle 1 and will be assessed 1 1 1 1 1 1 al al 1 1 1 1 olling additional subjects in Phase 2.**~~

Patients 12 years of age and older, with the exception of thyroid cancer and medullary thyroid cancer, and patients under 12 years of age regardless of cancer diagnosis, in principle and at investigator discretion, will be hospitalized during Cycle 1.

Section 3.2 Phase 2 Dose Expansion Cohort

Table 3-2 Disease Criteria for Enrollment: Cohorts 1 to 4

Cohort	Disease Criteria
Cohort 1	RET fusion-positive solid tumor (excluding CNS primary) with measurable disease
Cohort 2	RET-mutant MTC with measurable disease
Cohort 3	RET fusion-positive primary CNS tumor with measurable disease
Cohort 4	Any patient with RET mutation/alteration not fitting Cohort 1 to 3 criteria (i.e., RET alterations via plasma cfDNA or non- CLIA certified test, measurable or non-measurable disease)

Abbreviations: cfDNA = circulating free DNA; CNS = central nervous system; MTC = medullary thyroid cancer; RET = rearranged during transfection.

JAPAN ONLY:

~~Subjects in Japan will be hospitalized during Cycle 1 in Phase 1.~~

~~If a subject in Japan has not been enrolled in Phase 1 Dose Escalation, at least 1 subject in Phase 2 is required to be monitored by hospitalization during Cycle 1 and will be assessed by SRC to • √“ ×) ≥) z”≥•)hc 8QU8Td1)y ≤) „≥ yz“;“)z≥√ ≥)≥ „;“)y≤≤“ “ y,) z”≥•)“)h y ≥) 2.~~

Patients 12 years of age and older, with the exception of thyroid cancer and medullary thyroid cancer, and patients under 12 years of age regardless of cancer diagnosis, in principle and at investigator discretion, will be hospitalized during Cycle 1.

Section 4.1 Inclusion Criteria

14. Willingness of male and female patients with reproductive potential to utilize double effective birth control methods, defined as one used by the patient and another by his/her partner, for the duration of treatment and for ~~1 month~~ 3 months following study completion.

For male patients with a non-pregnant female partner of child-bearing potential, and woman of child-bearing potential, one of the following highly effective birth control methods (with a failure rate of less than 1% per year when used consistently and correctly) are recommended:

a) Combined estrogen and progestogen containing hormonal contraception associated with inhibition of ovulation given orally, **intravaginally*,** or **transdermally***

b) Progestin-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: considered a highly effective method only if defined as refraining from heterosexual intercourse during an entire period of risk associated with the study treatment. The reliability of sexual abstinence will be evaluated in relation to the duration of the study and to the usual lifestyle of the patient.

Birth control methods ***unacceptable*** for this clinical trial are:

e) Periodic abstinence (calendar, sympto-thermal, or post-ovulation methods)

f) Withdrawal (coitus interruptus)

g) Spermicide only

h) Lactational amenorrhea method

*** These methods are not approved for use in Japan.**

Study Assessments(for Japan only)

JAPAN ONLY:

~~Subjects in Japan will be hospitalized during Cycle 1 in Phase 1.~~

~~If a subject in Japan has not been enrolled in Phase 1 Dose Escalation, at least 1 subject in Phase 2 is required to be monitored by hospitalization during Cycle 1 and will be assessed by SRC to • √“ ×) ≥) z”≥•)hc 8)QU8)T d1)y ≤) ,≥ yz“;“)z≥√ ≥)≥ „;“)y≤≤““ y,) z”≥•)“)h y ≥) 2.~~

Patients 12 years of age and older, with the exception of thyroid cancer and medullary thyroid cancer, and patients under 12 years of age regardless of cancer diagnosis, in principle and at investigator discretion, will be hospitalized during Cycle 1.

Appendix N Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Protocol Synopsis.

Amendment [10] (09 October 2024)

This amendment is considered to be nonsubstantial.

Overall Rationale for the Amendment:

The purpose of this amendment is to

- add instructions for IP dispensing during Continued Access
- decrease frequency of Assessment Committee meetings
- minor corrections and edits for clarity.

• Section # and Name	Description of Change	Brief Rationale
5.1 Investigational Product	Removed columns for vehicles, CCI [redacted] from the intervention table	As no longer applicable
7.13.1 Tumor Measurements	Added "or MRI" and "(or CT / PET)" is in all sections of Section 7.13.1 where appropriate	For correction and to maintain consistency in including an MRI or CT (or CT / PET) imaging techniques for the baseline tumor assessment
9.5.1 Assessment Committee	Decreased frequency of Assessment Committee review meetings	Due to amount of safety data accrued in selpercatinib development program
Appendix K Continued Access	Added footnote "b" for instructions for IP dispensing during Continued Access	To provide clear instruction and ensure patients continue to receive the necessary treatment without interruption
Appendix M Country-specific Requirements	For France appendix, added Section 5.3.4.7 Substrates of BCRP and P-gp	To comply with France requirements for precautions of use with the BCRP and P-gp substrates with narrow therapeutic index.
	For patients enrolled in the UK and Canada, added assessment for thyroid function tests, menarche, and CCI palatability and acceptability in the Schedule of Assessments in the Canada and UK appendix, respectively	Correction for inadvertently missed assessments that should be collected as per the global Schedule of Assessments in Appendix A

Section # and Name	Description of Change	Brief Rationale
	For Canada appendix, strikethrough language that is not applicable for Inclusion Criteria Number 1	Correction
	For S y y≤y)y ≥ ≤“ 8)“) k “) Table 2: Serum Creatinine by Age y ≤)X≥ ≤)√)B) ≥y)y ≤)yz ≥ added rows for patients aged 2 to <6 years and 6 to <10 years	Correction for content that was inadvertently omitted
	For Canada appendix, in Synopsis Table 2 and Table 4-A)√) Serum Creatinine by Age and Gender for 2 ≥y)y ≤)yz ≥ changed from 12 to <13 years to 10 to <13 years in the age column	Correction

Amendment [9] (15 August 2023)

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 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
PROTOCOL SYNOPSIS	Added Regulatory Agency Identifier Numbers Ethical Considerations of Benefit/Risk	Compliance with EU-CTR
LIST OF ABBREVIATIONS AND DEFINITION OF TERMS	Added abuse GDPR IMP medication error misuse SUSAR	Compliance with EU-CTR
5.1. Investigational Product	Updated authorization as defined by EU-CTR for selpercatinib and the definition for study intervention Added a statement on packaging and labeling	Compliance with EU-CTR
5.2.4. Dose Modifications	Updated dose modification guidance for specific AEs	As per updated Investigator Brochure

Section # and Name	Description of Change	Brief Rationale
Table 5-1 Toxicities Requiring Dose Modification		
7.11.7. Thyroid Function	Added new section for thyroid function	As per updated Investigator Brochure
8. ADVERSE EVENTS	Updated events meeting the AE definition Updated regulatory reporting of SAEs	Compliance with EU-CTR
9.2. Analysis Populations	Added a statement on handling of missing, unused, and spurious data	Compliance with EU-CTR
10.1.4. Investigator Reporting Requirements	Added reporting to the sponsor or designee significant issues related to participant safety, participant rights, or data integrity	Compliance with EU-CTR
10.2.1. Data Protection	Added required language on data protection	Compliance with EU-CTR
10.4. Termination	Added required language for communication of suspended or terminated dosing and time frame for posting of summary of results as specified by local law or regulation	Compliance with EU-CTR
Appendix A Study Assessments Table 11-1. Schedule of Assessments	Revised evaluation for "Patients with MTC OR OTHER THYROID CARCINOMA ONLY: TSH" to "Thyroid Hormone (TSH and T4 or free T4 per local standard)"and removed the timepoint assessment at Cycle 1	Alignment with Section. 7.11.7 Thyroid Function
Throughout	Minor editorial and document formatting revisions	These are minor changes; therefore, they have not been summarized.

Amendment [8] (30 June 2023)

The amendment is considered to be substantial because it is likely to have a significant impact on the reliability and robustness of the data generated in the clinical study.

Overall Rationale for the Amendment:

The purpose of this amendment is to

- add the evaluation of a CCI formulation
- add the option of treatment holiday for patients with prolonged disease control, and
- include minor edits and correction.

Section # and Name	Description of Change	Brief Rationale
Protocol Synopsis	Exploratory objectives updated in Phase 1	For adding evaluation of CCI formulation

Section # and Name	Description of Change	Brief Rationale
	Secondary and exploratory objectives updated in Phase 2 Statement added under Inclusion Criterion 8 that patients having received selpercatinib previously are not eligible CCI added under INVESTIGATIONAL DRUG	For clarification For adding evaluation of CCI formulation
1.3 Role of RET in Pediatric Cancers	Cancer has been removed from statement regarding anti-RET multikinase inhibitors	For clarification
1.5.1 Pharmacokinetics	Data about bioequivalence in healthy volunteers added and prior data updated	Updated per new information
1.5.6 Known and Anticipated Risks	Adverse events updated	As per updated Investigator Brochure
1.5.7 Rationale for Selection of the Starting Dose	Table 1-2 and 1-3 updated	Pharmacokinetic parameters revised
2.1 Phase 1 Study Objectives	Exploratory objectives updated	For adding evaluation of CCI formulation
2.2 Phase 2 Study Objectives	Secondary and exploratory objectives updated	For adding evaluation of CCI formulation
3.1.1 Study Design	Statement about selpercatinib being administered as CCI form added	For adding evaluation of CCI formulation
3.3 General Treatment Procedures	Information about alternate formulation of selpercatinib added for patients under 18 years of age	For adding evaluation of CCI formulation
4.1 Inclusion Criteria	Statement added in Criterion 8 that patients who have received selpercatinib previously are not eligible	For clarification
5.1 Investigational Product	Information about CCI added and information about suspension removed	For adding evaluation of CCI formulation
5.2.1 General Dosing Instructions	Information about CCI and drug diary added	For consistency across all sections of protocol
5.2.4 Dose Modifications	Table 5-1 Toxicities Requiring Dose Modification updated to include Interstitial Lung Disease/Pneumonitis Adverse Event	As per updated Investigator Brochure
5.2.5 Drug Treatment Holiday	Information about drug treatment holiday added	As per investigator feedback
6.1 Removal of Patients from Therapy or Assessment	Information about disease progression during drug treatment holiday added	As per rationale of the amendment
7.12 Pharmacokinetic Samples: Blood (and Cerebrospinal Fluid, if Appropriate)	Information added cycles of PK data added	For consistency across all sections of protocol
7.13.1 Tumor Measurements	Information about patients with MIBG non-avid disease to undergo assessments added	For clarification

Section # and Name	Description of Change	Brief Rationale
7.14 Study Drug Administration and Dosing Diary	Diary information added	For consistency across all sections of protocol
7.14.1 Formulation Acceptability and Palatability Assessments	Information about acceptability and palatability questionnaires added	For adding evaluation of CCI formulation
7.14.1 Formulation Acceptability and Palatability Assessments	Questionnaire for CCI acceptability assessment added for patients	For adding the evaluation of CCI formulation
7.17 End of Treatment Visit	Window period updated	For clarification
9.1.2.2 Secondary	Endpoint about CCI assessment and palatability added	For adding evaluation of CCI formulation
9.1.1.3 and 9.1.2.3 Exploratory	Exploratory endpoints updated	For consistency across all sections of protocol
9.6 Efficacy Analyses	Information about patients experiencing disease progression during drug holiday added	For consistency across all sections of protocol
9.7 Pharmacokinetic Analyses	Pharmacokinetic of CCI added	For adding the evaluation of CCI formulation
9.8 Pain CCI	Logistic regression added	For clarification
Appendix A Study Assessments	Table 11-1 Schedule of Assessments updated with following: • Duration of window period for End of Treatment • Vital signs added at long-term follow up visit. • Menarche date collection for female patients added • Patient palatability and acceptability questionnaires added • Footnote t revised to add information about drug holiday	For safety assessment clarification
Appendix B Pharmacokinetic Sample Collection	Information about CCI formulation added	For adding evaluation of CCI formulation
Appendix H Selpercatinib Oral Suspension Dose Rounding	CCI dose rounding included	For adding evaluation of CCI formulation
Appendix K Continued Access	Information about long term safety for select patients added	For clarification
Appendix M Country-specific Requirements	Requirements for UK, Canada, and Japan added	For EU CTR consolidation

Section # and Name	Description of Change	Brief Rationale
Throughout	Minor editorial and document formatting revisions.	These are minor changes; therefore, they have not been summarized.

Signature Page for VV-CLIN-076219 v4.0

Approval	PPD Director 21-Feb-2025 14:04:51 GMT+0000

Approval	PPD 21-Feb-2025 18:18:13 GMT+0000

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