Statistical Analysis Plan: J2G-OX-JZJJ

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

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1. Statistical Analysis Plan for Clinical Study LOXO-RET-18036 (Lilly J2G-OX-JZJJ): A Phase 1/2 Study of the Oral RET Inhibitor Selpercatinib (LOXO-292) in Pediatric Patients with Advanced Solid or Primary Central Nervous System Tumors

Selpercatinib (LY3527723; LOXO-292)

This is a Phase 1/2, multicenter, open-label study that will include a dose escalation and a dose expansion phase. The purpose of Study J2G-OX-JZJJ is to assess the safety, tolerability and efficacy of selpercatinib (Loxo-292) when administered to pediatric patients with advanced solid tumor or primary central nervous system tumor.

Eli Lilly and Company
Indianapolis, Indiana USA 46285

Protocol LOXO-RET-18036 (J2G-OX-JZJJ)
Phase 1/2

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3. Revision History

Statistical analysis plan (SAP) Version 1 was approved 02 October 2020 prior to the first safety review.

SAP Version 2 was approved on 17 January 2023.Changes are summarized below:

- Added to the list of secondary endpoints an assessment of selpercatinib when given in CCI formulation.
- Added some clarifications regarding the phase 2 sample size in Section 6.
- Added definitions and clarifications to Section 8.5 (Pain and Health Related Quality of Life).

Changes for SAP Version 3 were approved on August 13, 2024. Changes are summarized below:

- Added content specific to the planned final analysis based on a planned final database lock of 2024, including alignment of objectives to protocol updates.
- The final approval date for SAP Version 3 document can be seen on page 1.

4. Study Objectives and Endpoints

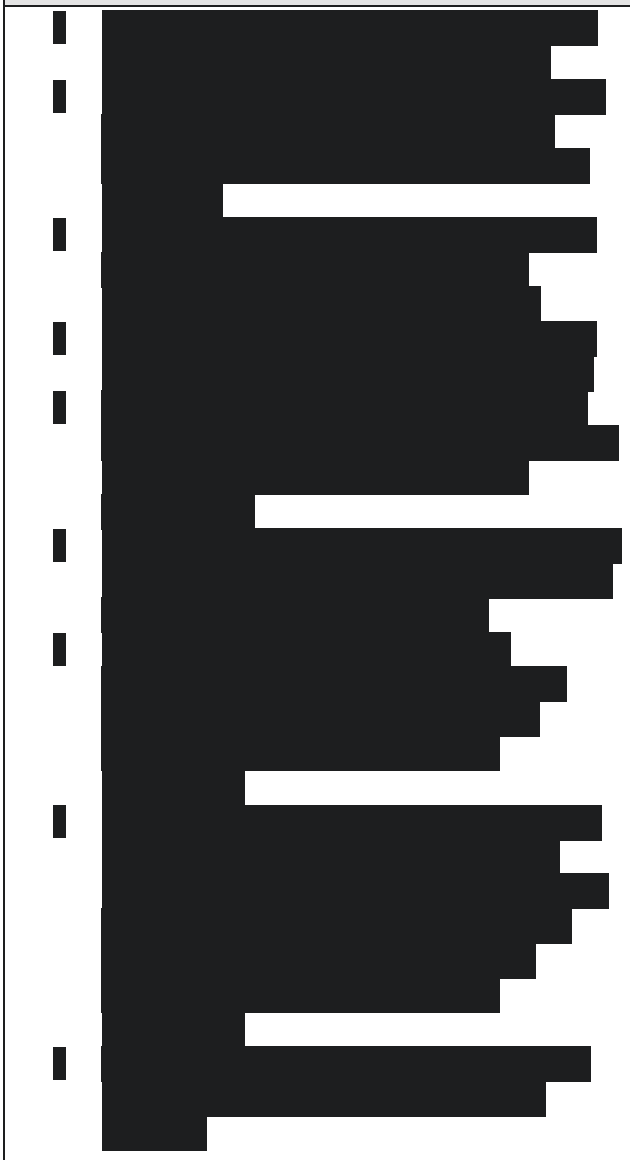
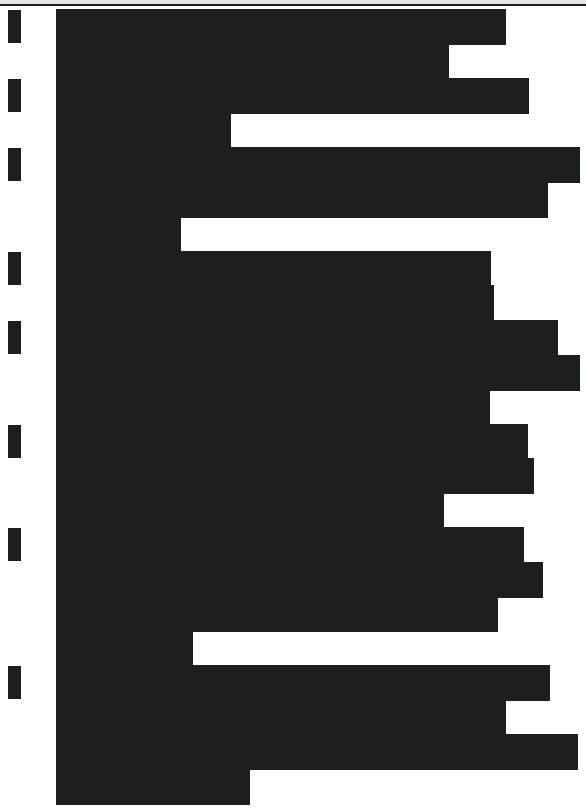
4.1. Phase 1 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To determine the safety, including DLTs, of the oral RET inhibitor selpercatinib in pediatric patients with an advanced solid or primary CNS tumor harboring an activating RET alteration.	• Frequency, severity, and relatedness of TEAEs and SAEs, including DLTs in pediatric patients receiving selpercatinib
Secondary	
• To characterize the PK properties of selpercatinib in pediatric patients with advanced solid, or primary CNS tumors harboring an activating RET alteration. • To identify the MTD and/or the appropriate dose of selpercatinib for further clinical investigation in this patient population. • To describe the antitumor activity of selpercatinib in pediatric patients with advanced solid or primary CNS tumors harboring an activating RET alteration.	• 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 MTD and/or the RP2D of selpercatinib in the 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
CCI	
[redacted]	[redacted]

Abbreviations: AUC 0-24 = area under the concentration versus time curve from time 0 to 24 hours;
CBR = clinical benefit rate; C_{max} = maximum drug concentration; CNS = central nervous system;
DLT = dose-limiting toxicity; CCI IRC = independent review committee;
MTD = maximum tolerated dose; ORR = objective response rate;
PedsQL-Core = Pediatrics Quality of Life - Core Module; PK = pharmacokinetic;
RANO = Response Assessment in Neuro-Oncology; RECIST = Response Evaluation Criteria in Solid Tumors;
RET = REarranged during Transfection;RP2D = recommended Phase 2 dose; SAE = serious adverse event;
TEAE = treatment-emergent adverse event; T_{max} = time to maximum plasma concentration.

4.2. Phase 2 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To determine the ORR as determined by an IRC and measured by the proportion of patients with best overall confirmed response of CR PR by RECIST 1.1, or RANO criteria, as appropriate, following treatment with selpercatinib in pediatric patients with an advanced cancer harboring an activating RET alteration.	• ORR based on RECIST 1.1 or RANO as appropriate to tumor type as determined by an IRC
Secondary	
• To determine the following in patients with advanced cancer harboring an activating RET alteration: o ORR based on the treating investigator's response assessment using RECIST 1.1 or RANO criteria, as appropriate to tumor type o DOR in patients with best overall response of CR or PR as determined by 1) an IRC and 2) the treating investigator o PFS following initiation of selpercatinib by 1) an IRC and 2) the treating investigator o OS following initiation of selpercatinib o To evaluate the CBR based on the proportion of patients with best overall response of CR, PR, or 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	• ORR based on RECIST 1.1 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. • Assessment of CCI [redacted] presentation, including acceptability and palatability by patient and/or caregiver

• 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 • [redacted]	
CCI [redacted]	
	

Abbreviations: AUC 0-24 = area under the concentration versus time curve from time 0 to 24 hours;
BOR = best overall response; CBR = clinical benefit rate; CEA = carcinoembryonic antigen;
C_{max} = maximum drug concentration; CR = complete response; DNA = deoxyribonucleic acid;
DOR = duration of response; ECG = electrocardiogram; CCI
IRC = independent review committee; MTC = medullary thyroid cancer; NGS = next generation sequencing;
ORR = objective response rate; OS = overall survival; PedsQL-Core = Pediatrics Quality of Life - Core Module;
PFS = progression-free survival; PK = pharmacokinetic; PR = partial response;
RANO = Response Assessment in Neuro-Oncology; RECIST = Response Evaluation Criteria in Solid Tumors;
RET = REarranged during Transfection; SAE = serious adverse event; SD = stable disease;
TEAE = treatment-emergent adverse event; T_{max} = time to maximum plasma concentration.

5. Study Design

This is a multicenter, open-label study of the Rearranged during Transfection (RET) inhibitor selpercatinib (LOXO-292) in pediatric patients with an advanced solid tumor or a primary central nervous system (CNS) tumor. The study is divided into a Phase 1 and Phase 2 component.

5.1. Phase 1 Dose Escalation

This trial will use a CCI -dose escalation CCI . Selpercatinib is administered orally twice daily (BID), with the dose adjusted by body surface area (BSA). BSA will be determined by the Mosteller (√((height (cm) × weight (kg))/3600)) formula (Mosteller 1987). The starting dose level is intended to deliver equivalent exposure to the recommended Phase 2 dose (RP2D) in CCI . A minimum of [redacted] patients will be enrolled in an open cohort, depending on the occurrence of dose-limiting toxicity (DLTs). Escalation will proceed through the planned dose levels, or until the maximum tolerated dose (MTD) or RP2D is reached, or until the sponsor determines that a suitable dose has been achieved based on pharmacokinetic exposure and toxicity. Each patient must have completed 28 days of safety assessment in Cycle 1 (C1), and have received at least 75% of the planned total dose to be eligible for the assessment of DLT.

A detailed description of the Phase 1 study design is contained in Protocol JZJJ.

5.2. Phase 2 Dose Expansion

Phase 2 is an expansion study in 4 selected cohorts of pediatric patients. Approximately 10 to 20 patients may enroll into each of the 4 cohorts listed. 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.

Table JZJJ.5.1. 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 (that is, RET alterations via plasma CCI , non-measurable [that is, only evaluable] disease)

Abbreviation: CCI CNS = central nervous system; MTC = medullary thyroid cancer; RET = REarranged during Transfection.

Due to the actual pattern of enrollment, summary statistics will not be calculated by Cohorts 1 to 4 and instead will generally be performed and reported overall and separately for patients with (i) *RET*-mutant MTC, (ii) *RET* fusion-positive papillary thyroid cancer (PTC), and (iii) other *RET* fusion-positive tumors. See Section 8.1 for details.

Selpercatinib is administered in oral capsule, oral CCIt, or a liquid suspension at the recommended dose determined in Phase 1. Cycles are 28 days of continuous BID dosing. Patients undergo periodic radiologic evaluation and ongoing safety assessments as outlined in Protocol JZJJ.

6. Sample Size Determination

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 a dose level is evaluated for MTD/RP2D and the sponsor declares 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 overenrolled 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. [redacted]

Phase 2

Approximately [redacted] patients may be enrolled in each of the designated Phase 2 cohorts: [redacted] Additional patients may be enrolled to better characterize the safety and efficacy of the selpercatinib RP2D.

The number of patients was determined largely by feasibility considerations owing to the extreme rarity of pediatric patients with an advanced cancer harboring an activating RET alteration. Although the planned sample size is limited, it is anticipated that the objective response rate may be high (≥50%) for each cohort evaluated. Any summary of objective response rate (ORR) for a group of at least 20 patients is estimated to provide approximately 75% power to achieve a lower boundary of a 2-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 advanced disease.

7. Analysis Sets

Population	Description
Enrolled	Patients who have signed the informed consent / assent document
Safety	All enrolled patients who received at least 1 dose of selpercatinib. This population will be used for both safety and efficacy analysis.

8. A Priori Statistical Methods

8.1. General Considerations

Statistical analysis of this study will be the responsibility of Lilly or its designee. All CIs will be given at a 2-sided 95% level, unless otherwise stated. Statistical analysis will be performed using SAS software (SAS, version 9.1.2 or higher).

Continuous variables will be summarized using descriptive statistics (that is, the number of patients, mean, median, standard deviation, minimum, and maximum). Categorical variables will be summarized by frequency and its corresponding percentage.

As described in Section 5.2, summaries of safety, baseline characteristics, and efficacy will generally be performed and reported overall and separately for patients with (i) *RET*-mutant MTC, (ii) *RET* fusion-positive papillary thyroid cancer (PTC), and (iii) other *RET* fusion-positive tumors.

Considering that Study JZJJ is primarily conducted in pediatric patients, additional data summaries and listings will be subgrouped specifically by categories of age at study entry. One set of summaries of patients by age will be grouped according to these categories:

≥ 6 months and < 2 years
≥ 2 years and < 12 years
≥ 12 years and < 18 years, and
≥ 18 years.

A second complete set of summaries of patients by age will be grouped according to these categories:

≥ 6 months and < 2 years
≥ 2 years and < 6 years
≥ 6 years and < 12 years
≥ 12 years and < 18 years, and
≥ 18 years.

Data summaries or listings may be performed specific to certain geographical considerations (for example,. summaries or listings of patients enrolled in east Asian countries).

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

8.1.1. Definitions

Definitions of efficacy and safety analysis variables are listed in respective sections of the SAP. Other variables are listed below alphabetically:

Baseline Measurement: unless otherwise specified, the last nonmissing measurement prior to the first dose of selpercatinib.
Duration: duration is calculated as

- duration (days): (end date – start date + 1)
- duration (weeks): (end date – start date + 1)/7
- duration (months): (end date – start date + 1)/30.4375
  (days in months = (1/12) × average number of days in a year)
- duration (years): (end date – start date + 1)/365.25

Study Day: study day is calculated as assessment date – first dose date + 1 day if the assessment is done on or after the first dose day. If the assessment is done prior to the first dose day, study day will be calculated as assessment date – first dose date. Date of first dose is defined as Study Day 1.
Time-to-Event: the event or censoring time (days) is calculated as date of event/censoring – first dose date + 1.

8.1.2. Handling of Dropouts or Missing Data

All analyses and descriptive summaries will be based on the observed data. Unless otherwise specified, missing data will not be imputed or carried forward. Rules for handling dropouts or missing data are listed by type of analysis alphabetically.

Adverse event (AE) or concomitant therapy

- The missing day of onset of an AE or start date of a concurrent therapy will be set to
  - first day of the month that the event occurred, if the onset yyyy-mm is after the yyyy-mm of first study treatment
  - the day of the first study treatment, if the onset yyyy-mm is the same as yyyy-mm of the first study treatment, or
  - the date of informed consent, if the onset yyyy-mm is before the yyyy-mm of the first treatment.
- The missing day of resolution of an AE or end date of a concurrent therapy will be set to
  - the last day of the month of the occurrence. If the patient died in the same month, then set the imputed date as the death date.
- If the onset date of an AE or start date of a concurrent therapy is missing both the day and month, the onset date will be set to
  - 01 January of the year of onset, if the onset year is after the year of the first study treatment
  - the date of the first treatment, if the onset year is the same as the year of the first study treatment, or
  - the date of informed consent, if the onset year is before the year of the first treatment.

- If the resolution date of an AE or end date of a concurrent therapy is missing both the day and month, the date will be set to
  - 31 December of the year of occurrence. If the patient died in the same year, then set the imputed date as the death date.
- If the date is completely missing, then no imputation will be done and the event will be considered as treatment-emergent with unknown onset date, unless the end date rules out the possibility.

Diagnosis date, the following conventions will be used for imputing partial dates:

- If only the day of the month is missing, the 15th of the month will be used to replace the missing day.
- If both the day and the month are missing, 01 July will be used to replace the missing information.

General rule for imputing other dates:

- If only the day is missing, then assign Day 15 of the month, or the date of death if the patient died prior to 15th of the same month to the day.
- If the month is missing, then the date will be set to 01 July of the year, or the date of death if the patient died prior to 01 July of the same year.

However, in all cases, after imputation, check if the imputed date is logically consistent with other relevant date variable(s) and make an appropriate correction if necessary.

Relationship: missing classifications concerning relationship will be considered as related to study medication.
Time-to-event analysis: all censored data will be accounted for using appropriate statistical methods.

8.2. Patient Information

8.2.1. Disposition of Patients

A detailed description of patient disposition will be provided according to the Consolidated Standards of Reporting Trials publishing requirements, including a summary of the number and percentage of patients entered into the study and treated, as well as number and percentage of patients completing the study, or discontinuing (overall and by reason for discontinuation). If known, a reason for their discontinuation for both study treatment and study will be given.

8.2.2. Demographics and Other 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.

Age will be calculated in years relative to the enrollment date based on the following definition: (informed consent date - date of birth + 1)/365.25; birth month and day are imputed to be 01 July

if only birth year is collected through the electronic case report form; birth day is imputed to be the 15th of the month if only birth year and month are collected.

Summaries will include but not be restricted to the following parameters:

standard demographics (age, sex, race, ethnicity, height, weight, BSA using the Mosteller formula, Lansky or Karnofsky performance status as appropriate)
cancer and other relevant medical history (primary tumor, time from initial diagnosis, stage at start of treatment, extent of disease, etc.)
RET alteration type (fusion, mutant, other, none) and subtype (for example, fusion partners, specific mutation), and
prior cancer treatments.

8.3. Efficacy Analyses

This section describes the statistical methods to be used for the efficacy analyses. In general efficacy analyses will be summarized overall and by tumor type and age as described in Section 8.1. Other (retrospective and exploratory) efficacy analyses may be performed if deemed to be of regulatory or clinical interest.

8.3.1. Tumor Response

Best overall response (BOR) for each patient (complete response [CR], partial response [PR], stable disease [SD], progressive disease, or inevaluable), occurring between the first dose of selpercatinib and the date of documented disease progression or the date of subsequent therapy or surgical intervention, will be determined based on disease-specific response criteria and used for analysis (for example, Response Evaluation Criteria in Solid Tumors [RECIST] v1.1 criteria for patients with solid tumors or the Response Assessment in Neuro-Oncology [RANO] system for patients with primary CNS tumors as outlined in Appendix 2 and Appendix 3, respectively). All objective responses will be confirmed by a second scan 28 days after the initial response. BOR will be summarized descriptively to show the number and percentage of patients in each response category.

Waterfall plots will be used to graphically depict the maximum decrease from baseline in the sum of diameters of target lesions. Spider plots and swimmer plots should be created to display the change in tumor burden over time for individual patients and the occurrence of clinical outcomes of interest (for example, tumor response, disease progression, treatment discontinuation, and death). Kaplan-Meier summary tables and figures should be created for DoR, PFS, and OS as defined below.

Objective response rate (ORR) is defined as the proportion of patients who achieve a BOR of CR or PR. Patients who do not have any postbaseline tumor response assessments are considered nonresponders and are included in the denominator when calculating the response rate.

Clinical benefit rate (CBR) is defined as the proportion of patients who achieve a BOR of CR, PR, or SD lasting 16 or more weeks following initiation of selpercatinib.

Duration of response (DOR) is defined as the time from the date that measurement criteria for CR or PR (whichever is first recorded) are first met and subsequently confirmed, until the first date that disease is recurrent or documented disease progression is observed, or the date of death from any cause in the absence of documented disease progression or recurrence. The DOR will be analyzed for patients who achieve a BOR of CR or PR.

The ORR and CBR, with exact 95% CI by Clopper-Pearson, will be summarized. DOR will be summarized descriptively using the Kaplan-Meier method with the 95% CI about the median calculated using the Brookmeyer and Crowley method. Median follow-up for DOR will be estimated according to the Kaplan-Meier estimate of potential follow-up (Schemper and Smith 1996). The primary analysis of ORR will be based on the responses determined by an independent review committee (IRC). A secondary analysis of ORR will be based on the treating investigator's assessment. CBR and DOR will also be analyzed based on the IRC and the treating investigator as secondary endpoints.

8.3.2. Progression-Free Survival

Progression-free survival (PFS) is defined as the time from the date of the first dose of selpercatinib until the occurrence of documented disease progression by the RECIST 1.1 criteria for primary solid tumors or by the RANO system for CNS primary tumors, or death from any cause in the absence of documented progressive disease. Patients known to be alive and without disease progression will be censored at the time of the last adequate tumor assessment. Table JZJJ.8.1 defines censoring rules to be applied to the PFS analysis.

The Kaplan-Meier estimate of the median PFS and the corresponding 95% CI calculated using the Brookmeyer and Crowley method will be presented. The Kaplan-Meier estimates of the PFS rates and the corresponding 95% CI using the Greenwood's formula will also be provided by 6-month intervals. A plot of the Kaplan-Meier estimate of the survival distribution function over time for PFS will be presented. Median follow-up for PFS will be estimated according to the Kaplan-Meier estimate of potential follow-up (Schemper and Smith 1996). The analysis of PFS will be based on the responses determined by an IRC and on the treating investigator's assessment.

Table JZJJ.8.1. Censoring Scheme

Situation	Event/Censor	Date of Event or Censor
Tumor progression or death	Event	Earliest date of PD or death
No tumor progression and no death	Censored	Date of last adequate tumor assessment[a] or date of the first dose (whichever is later)
Unless		
No baseline radiologic tumor assessment available	Censored	Date of the first dose
No adequate postbaseline tumor assessment available and death reported after 2 scan intervals[b] following the first dose	Censored	Date of the first dose
New anticancer therapy and no tumor progression or death within next 14 days	Censored	Date of adequate tumor assessment prior to (start of new therapy + 14 days) or date of the first dose (whichever is later)
Tumor progression or death documented immediately after 2 or more consecutively missing scan intervals following last adequate tumor assessment or the first dose (whichever is later)	Censored	Date of last adequate tumor assessment or date of the first dose (whichever is later)

Abbreviations: CR = complete response; PD = progressive disease; PFS = progression-free survival; PR = partial response; RANO = Response Assessment in Neuro-Oncology; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease.

Note: If there are multiple dates associated with 1 assessment, the assessment date will be set to the first date when the overall response is PD and the last date otherwise.

[a] Adequate tumor assessment per RECIST 1.1/RANO criteria refers to an assessment with one of the following responses: CR, PR, SD, or PD.

[b] The 2-scan interval is counted from the date of last adequate tumor assessment to the date of next 2 scheduled tumor assessments plus 14 days (adjusted by tumor assessment window).

8.3.3. Overall Survival

Overall survival (OS) is defined as the time from the date of the first dose of selpercatinib until death from any cause. If the patient is alive or lost to follow-up at the time of data analysis, OS data will be censored on the last date the patient is known to be alive. The Kaplan-Meier estimate of the median OS and the corresponding 95% CI calculated using the Brookmeyer and Crowley method will be presented. The Kaplan-Meier estimates of OS rates and the corresponding 95% CI using the Greenwood's formula will also be provided by 6-month intervals. Plots of the Kaplan-Meier estimate of the survival distribution function over time for OS will be presented. Median follow-up for OS will be estimated according to the Kaplan-Meier estimate of potential follow-up (Schemper and Smith 1996).

8.4. Pharmacokinetic Analyses

Pharmacokinetic (PK) parameters such as maximum drug concentration (C_{max}) and area under the curve (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.

Details of the pharmacokinetic analysis may be found in a separate pharmacokinetic SAP.

8.5. 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 (PRO) instrument at that visit.

In patients 3 years of age or older, pain will be assessed by the Wong-Baker Faces Scale (WBFS). CCI [redacted] Proportions of patients who have improved, stable, and deterioration on pain scores will be reported by time point. Changes in WBFS pain score of 2 points or more from baseline are considered clinically meaningful change for both improvement and deterioration. Change from baseline in the patient-reported pain score will be calculated at the BOR visit CCI [redacted] CCI [redacted]

The health-related quality of life (HRQoL) assessment will be based on the Pediatrics Quality of Life - Core Module (PedsQL-Core) for the patient or their parent/caregiver. CCI [redacted] Proportions of patients who have improved, stable, and deterioration on PedsQL total scores will be reported by time point. Changes in the PedsQL total score of 4.5 points or more from baseline are considered clinically meaningful change for both improvement and deterioration. CCI [redacted] Summaries for domain scores will be performed by domain-specific criteria to determine improvement/deterioration (for example, changes in physical functioning of 6.9 points or more, emotional functioning of 7.8 points or more, social functioning of 9.0 points or more, and school functioning of 9.7 points or more). CCI [redacted]

Adverse events (AEs) may have an effect on patient-reported pain and HRQoL. Presence of grade 3 or higher AEs for diarrhea and fatigue, as defined by the National Cancer Institute - Common Terminology Criteria for Adverse Events (NCI-CTCAE), with a start date within 2 weeks prior to PRO evaluation or ongoing during PRO evaluation will be tabulated versus the change in PedsQL-Core total score at the corresponding evaluation. If an association is found, an analysis adjusting for these effects will be performed.

8.6. Safety Analyses

In general, safety data will be tabulated and presented as described in Section 8.1.

Safety data from Study JZJJ will also be part of an integrated safety analysis from clinical studies that further characterize the potential serious risk of long-term adverse effects of selpercatinib on growth and development, including an assessment of growth plate abnormalities in a sufficient number of adolescent patients 12 years of age and older with RET mutant MTC and RET fusion-positive thyroid cancer. Patients will be monitored for growth and development using age-appropriate screening tools. Evaluations will include growth as measured by height, weight, height velocity and height standard deviation scores, age at adrenarche if applicable (males), age at menarche if applicable (females) and Tanner stage. Patient monitoring will be performed until discontinuation of study treatment or a minimum of 5 years from start of treatment, whichever occurs first.

8.6.1. Study Drug Exposure

The number of cycles received, dose omissions/withheld, dose reductions, and dose intensity for selpercatinib will be summarized. The exposure derivations are provided below.

duration of therapy (weeks) = (date of last dose of selpercatinib - date of first dose of selpercatinib + 1) ÷ 7
cumulative dose (mg) = sum of all doses
dose intensity (mg/week) = (cumulative dose) ÷ (duration of therapy)
planned dose intensity (mg/week) = daily dose (mg) × 7
relative dose intensity (%) = (dose intensity / planned dose intensity) ×100
cumulative dose by BSA (mg/m^2) = sum of (daily dose taken / BSA)

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

8.6.2. Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) preferred term (PT) derived from the verbatim term will be used when reporting AEs by MedDRA terms. The MedDRA lower level term will be used in the treatment-emergent computation. Severity will be measured using the grade defined by the NCI - CTCAE version 5.0.

Treatment-emergent adverse events (TEAEs) are events that first occurred or worsened in severity after the first dose of selpercatinib and up to 28-day safety follow-up visit. TEAEs will be summarized by system organ class (SOC) and by decreasing frequency of PT within SOC.

Serious adverse events (SAEs) are any AEs that results in any of these outcomes:

death
initial or prolonged inpatient hospitalization
a life-threatening experience (that is, immediate risk of dying)
persistent or significant disability/incapacity
congenital anomaly/birth defect, or
important medical events (detailed description is contained in the protocol).

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
treatment-emergent SAEs
drug-related treatment-emergent SAEs
Fatal/Grade 5 TEAEs
discontinuation of study drug due to TEAEs
discontinuation of study drug due to drug-related TEAEs
dose adjustments due to TEAEs
dose adjustments due to drug-related TEAEs, and
DLT.

The observed DLT rate in each Phase 1 dose cohort will be calculated by the crude proportion of patients who experienced DLT as defined in Protocol JZJJ. Multiple concurrent AEs leading to DLT will be considered a single DLT. The estimate of the DLT rate will be accompanied by a 2-sided 95% exact binomial CI by Clopper-Pearson.

8.6.3. Deaths

Summary / listing of deaths (all deaths and deaths on treatment / within 30 days from the last dose of selpercatinib) and their primary cause (study disease progression, AE, other). Listing of TEAEs leading to death.

8.6.4. 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 listed:

baseline value
minimum postbaseline value
maximum postbaseline value
average postbaseline value, and
last postbaseline value.

8.6.5. Vital Signs

The following vital signs were assessed for each study at screening and at periodic time points (including end of treatment and safety follow-up) following the initiation of selpercatinib:

systolic and diastolic blood pressures (mm Hg)
heart rate (beats per minute)
respiration rate (breaths per minute)
body temperature (degrees Celsius)
body weight (kg), and
height (cm).

Each of these vital signs will be summarized in a descriptive manner by calculating the mean, standard deviation, median, and range. The height will also be summarized by height velocity and height standard deviation scores according to the CDC's growth charts (Kuczmarski et al. 2002).

8.6.6. Electrocardiogram

A summary will be provided for patients who experienced QT interval corrected for heart rate using Fridericia's formula (QTcF) by categories. Changes in QTcF will be presented using a shift table analysis of baseline versus worst on-treatment value. Abnormal changes (also known as delta changes) of QTcF >60 msec will also be summarized.

8.6.7. Growth Plate Evaluation

Patients who have not yet obtained full adult height will undergo either x-ray or magnetic resonance imaging (MRI) of the right knee at baseline and every 6 months during participation in the study while the growth plate remains open. Growth plate abnormality after study baseline will be captured as an AE and summarized as described in Section 8.6.2.

Besides, the number and percentage of patients with growth plate open will be summarized.

8.6.8. 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. Delays to pubertal maturity (according to the Tanner Scale) after study baseline will be captured as an AE and summarized as described in Section 8.6.2.

Besides, pubic hair, breasts in females, and genitalia in males will be collected in stage for eligible patients. Changes in stage will be presented using a shift table analysis of baseline versus worst on-treatment value.

8.6.9. Performance Status

Performance status is graded according to either the Karnofsky or Lansky scales depending upon the patient's age. Data from both scales may be mapped to the Eastern Cooperative Oncology Group (ECOG) performance scale (0–5) to maximize uniformity (Appendix 4). Changes in performance status will be presented using a shift table analysis of baseline versus worst on-treatment score.

8.6.10. Concomitant Medications and Procedures

Concomitant medications are defined as medications that were started at any time prior to the discontinuation of selpercatinib and stopped at any time after the date of the first dose of selpercatinib. If it cannot be determined whether a medication was a prior medication due to partial medication start or end dates, the medication will be considered concomitant.

The reported medication term will be coded using the World Health Organization (WHO) Drug Dictionary version September 2018 or later. The number and percentage of patients taking concomitant medications will be summarized by generic term, sorted in decreasing order of frequency. All reported prior and concomitant medications will be listed by patient.

Concomitant procedures will be displayed in patient listing format.

8.6.11. Subsequent Anti-Cancer Therapy

The number and percentage of patients taking subsequent anticancer therapy and the type of subsequent anticancer therapy (chemotherapy, targeted therapy, surgery, radiation, and other) will be tabulated.

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

8.8. Palatability and Acceptability Analyses

Palatability and Acceptability for the selpercatinib CCI formulation will be assessed based on data derived from questionnaires collected from patients/caregivers. Listings and descriptive/summary statistics will be generated for analysis from the 2 timepoints of questionnaire collection. This data may be evaluated in the context of exposure data to understand if there is impact from the CCI formulation on administration compliance.

9. Interim Analyses

9.1. Assessment Committee

This is an open-label, Phase 1/2, pediatric study. An assessment committee (AC) will monitor safety-related data during the course of the trial on a regular basis. The AC members include a global principal investigator, an external physician, the sponsor's project physicians and the sponsor's compound lead statistician. 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. The purpose of the AC is to advise the sponsor regarding the continuing safety of study participants.

Details are contained in a separate AC charter.

9.2. Clinical Trial Registry Analyses

Additional analyses will be performed for the purpose of fulfilling the clinical trial registry (CTR) requirements. Analyses provided for the CTR requirements include the following:

Summary of AEs, provided as a dataset which will be converted to an XML file. Both SAEs and "Other" AEs are summarized by MedDRA PT.
An AE is considered "Serious" whether or not it is a TEAE.
An AE is considered in the "Other" category if it is both a TEAE and is not serious.
For each SAE and "Other" AE, the following are provided:

- the number of participants at risk of an event (if certain subjects cannot be at risk for some reason, for example, gender-specific AEs, then the number will be adjusted to only include the patients at risk)
- the number of participants who experienced each event term, and
- the number of events experienced.

For each SAE, the following are also provided for the EudraCT results submission:

- the number of occurrences (events) causally related to treatment
- the total number of deaths, and
- the number of deaths causally related to treatment.

Consistent with www.ClinicalTrials.gov requirements, a threshold for frequency of "Other" AEs can be implemented rather than presenting all "Other" AEs. For example, "Other" AEs that occur in fewer than 5% of patients may not be included if a 5% threshold is chosen. The frequency threshold must be less than or equal to the allowed maximum of 5%.
A participant flow will be created that will describe

- number of participants. Screen failures do not need to be included. Number of participants who did not complete the study. This analysis will be based on study discontinuation, not treatment discontinuation.
- reasons participants did not complete the study.

9.3. Development Safety Update Report

The following reports are needed for the development safety update report (DSUR):

estimated cumulative subject exposure
cumulative exposure to investigational drug by demographic characteristics
listing of subjects who died during the DSUR period, and
discontinuations due to AEs during the DSUR Period.

10. References

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11. Appendices

Appendix 1. List of Abbreviations

Term	Definition
AC	assessment committee
AE	adverse event
AUC	area under the curve
BID	twice daily
BOR	best overall response
BSA	body surface area
CBR	clinical benefit rate
CDC	Centers for Disease Control and Prevention
CI	confidence interval
C_{max}	maximum drug concentration
CNS	central nervous system
CR	complete response
CSR	clinical study report
CTR	clinical trial registry
DLT	dose-limiting toxicity
DOR	duration of response
DSUR	development safety update report
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
HRQoL	health-related quality of life
IRC	independent review committee
MedDRA	Medical Dictionary for Regulatory Activities
MTD	maximum tolerated dose
MRI	magnetic resonance imaging

Term	Definition
NCI-CTCAE	National Cancer Institute - Common Terminology Criteria for Adverse Events
ORR	objective response rate
OS	overall survival
PedsQL-Core	Pediatrics Quality of Life - Core Module
PFS	progression-free survival
PK	pharmacokinetic
PR	partial response
PT	preferred term
QTcF	QT interval corrected using Fridericia's formula
RANO	Response Assessment in Neuro-Oncology
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SOC	System Organ Class
TEAE	treatment-emergent adverse event

Appendix 2. Assessment of Disease Response Using RECIST, Version 1.1

A summary of the overall tumor response calculation made by the investigator at each time point is summarized in Table APP.2.1 for patients with target (± nontarget) disease, and Table APP.2.2 for patients with nontarget disease only. When no imaging/measurement is done at all at a particular time point, the patients will be considered inevaluable (NE) at that point. If only a subset of target or nontarget lesion measurements are made at an assessment, the patient will be considered NE at that time point unless the contribution of the individual missing lesion(s) would not change the assigned time point response (for example, if a patient has a baseline sum of 50 mm with 3 measured lesions and at a follow-up time point only 2 lesions are assessed, but these give a sum of 80 mm, the patient will have achieved progressive disease status, regardless of the contribution of the missing lesion).

Table APP.2.1. Time Point Response for Patients with Target ± Nontarget Disease

Target lesions	Nontarget lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD/not all evaluated	No	PR
Stable	Non-PD/not all evaluated	No	Stable
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Abbreviations; CR = complete response; NE = inevaluable; PD = progressive disease; PR = partial response.
Source: Eisenhauer et al. 2009

Table APP.2.2. Time Point Response for Patients with Nontarget Disease Only

Nontarget lesions	New lesions	Overall response
CR	No	CR
Non-CR/Non-PD	No	Non-CR/Non-PD[a]
Not all evaluated	No	NE
PD	Yes or No	PD
Any	Yes	PD

Abbreviations: CR = complete response; NE = inevaluable; PD = progressive disease.
[a] Non-CR/Non-PD refers to stable disease
Source: Eisenhauer et al. 2009

A summary of the best overall tumor response calculation is summarized in Table APP.2.3. For confirmation of CR and PR, the response criteria must be met again at least 4 weeks after the date of the initial documentation of response. Patients with time point responses such as PR–NE–PR or PR–Stable–PR will be considered confirmed.

Table APP.2.3. Best Overall Response

Overall response First time point	Overall response Subsequent time point	Best overall response
CR	CR	CR
CR	PR	Stable, PD, or PR[a]
CR	Stable	Stable provided that minimum criteria for Stable duration met. Otherwise PD.
CR	PD	Stable provided that minimum criteria for Stable duration met. Otherwise PD.
CR	NE	Stable provided that minimum criteria for Stable duration met. Otherwise PD.
PR	CR[b]	PR
PR	PR	PR
PR	Stable	Stable
PR	PD	Stable provided that minimum criteria for Stable duration met. Otherwise PD.
PR	NE	Stable provided that minimum criteria for Stable duration met. Otherwise PD.
NE	NE	NE

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

[a] If a CR is *truly* met at a first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response will depend on whether minimum duration of Stable is met. However, sometimes "CR" may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient has PR, not CR at the first time point. Under these circumstances, the original CR will be changed to PR and the best response is PR.

[b] Every effort will be made to confirm the CR. For such cases where CR is not subsequently confirmed, then best overall response is PR.

Source: Eisenhauer et al. 2009

Unless specified otherwise, tumor assessments will be excluded from the best overall response calculation if they occur after the start of nonprotocol anticancer therapy or surgical intervention. Patients who undergo surgical resection and have no viable tumor cells and negative margins on postsurgical pathology report will be considered complete responders by surgery/pathology. Such patients will continue to undergo assessments for disease recurrence following surgery.

Stable disease for best overall response will be reported as: 1) lasting less than 16 weeks; or 2) lasting 16 weeks or more; or 3) any duration. Stable disease will be measured from the date of the first dose of study drug until the criteria for disease progression is first met. A best overall

response of stable disease will require a time point response of stable disease or better at least 6 weeks after the initiation of study drug.

Best overall response will be classified as NE for patients with early progression or early death. Early progression will include patients who discontinue study drug due to worsening disease but without objective evidence of disease progression, and their best overall response cannot be determined because tumor assessments were either incomplete or were never performed or not repeated. Similarly, early death will include patients who die without objective evidence of disease progression beforehand, and their best overall response cannot be determined because tumor assessments were either incomplete or were never performed or were not repeated.

Appendix 3. Assessment of Disease Response Using RANO Criteria

Response Category	Criteria
Complete Response	Disappearance of all measurable and nonmeasurable enhancing disease Stable or improved nonenhancing 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 nonmeasurable disease Stable or improved nonenhancing 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 nonenhancing T2/FLAIR lesions not attributable to other nontumor causes Any new lesions Clinical deterioration no attributable to other nontumor causes and not due to steroid decrease
Stable Disease	Does not meet other criteria for response or progression Stable nonenhancing FLAIR/T2 lesions Clinically stable with stable or reduced corticosteroids compared to baseline

Source: Wen et al. 2010

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

clearly defined margins
visible on 2 or more axial slices, preferably <5 mm thick
at least 10 mm in size if slice thickness is <5 mm (or 2 times slice thickness if >5 mm), and
does not measure a cystic cavity.

Nonmeasurable 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 2 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 1 or 2 are increasing in size, the enlarging lesions should be considered the target lesions for evaluation of response.

Appendix 4. Performance Scales and ECOG Equivalent

Score	Karnofsky Description[1]	Lansky Description[2]	ECOG Equivalent[3]
100	Normal; no complaints; no evidence of disease	Fully active, normal	0
90	Able to carry on normal activity; minor signs or symptoms of disease	Minor restrictions in strenuous physical activity	
80	Normal activity with effort; some signs or symptoms of disease	Active, but tired more quickly	1
70	Cares for self; unable to carry on normal activity or do active work	Greater restriction of plan *and* less time spent in play activity	
60	Requires occasional assistance, but is able to care for most personal needs	Up and around, but active play minimal; keeps busy by being involved in quieter activities	2
50	Requires considerable assistance and frequent medical care	Lying around much of the day, but gets dressed; no active playing, participates in all quiet play and activities	
40	Disabled; requires special care and assistance	Mainly in bed; participates in quiet activities	3
30	Severely disabled; hospitalization is indicated, although death not imminent	Bed bound; needing assistance even for quiet play	
20	Very sick; hospitalization necessary; active support treatment is necessary	Sleeping often; play entirely limited to very passive activities	4
10	Moribund; fatal processes progressing rapidly	Doesn't play; doesn't get out of bed	
0	Dead	Unresponsive	5

Abbreviation: ECOG = Eastern Cooperative Oncology Group.

[1] For patients 16 years of age or older. Source: Karnofsky and Burchenal 1949

[2] For patients less than 16 years of age. Source: Lansky et al. 1987

[3] Source: CIBMTR 2009

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