Statistical Analysis Plan J2G-OX-JZJA (Version 3)

A Phase 1/2 Study of Oral Selpercatinib (LOXO-292) in Patients With Advanced Solid Tumors, Including RET Fusion-Positive Solid Tumors, Medullary Thyroid Cancer, and Other Tumors With RET Activation (LIBRETTO-001)

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Title Page

Protocol Title: A Phase 1/2 Study of Oral Selpercatinib in Patients with Advanced Solid Tumors, Including RET Fusion-positive Solid Tumors, Medullary Thyroid Cancer, and Other Tumors with RET Activation

Protocol Number: J2G-OX-JZJA

Compound Number: LY3527723 (Selpercatinib)

Short Title: A Phase 1/2 Study of Oral Selpercatinib in Patients with Advanced Solid Tumors

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Abbreviations and Definitions

Term	Definition
ADI	actual dose intensity
AE	adverse events
ALT	alkaline phosphatase, albumin, alanine transaminase
AST	aspartate aminotransferase
BOR	best overall response
CBR	clinical benefit rate
CEA	carcinoembryonic antigen
CI	confidence interval
CNS	central nervous system
CR	complete response
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DCR	disease control rate
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
IRC	independent review committee
Lilly	Eli Lilly and Company
MedDRA	Medical Dictionary for Regulatory Activities
MTC	medullary thyroid cancer
NE	not evaluable
NSCLC	non-small cell lung cancer
ORR	overall response rate
OS	overall survival
PD	progressive disease
PDI	planned dose intensity
PFS	progression-free survival
PR	partial response
QTcF	Fridericia's Correction Formula
RDI	relative dose intensity

Term	Definition
RECIST	Response Evaluation Criteria in Solid Tumours
RET	rearranged during transfection
SAE	serious adverse events
SAP	statistical analysis plan
SD	stable disease
TOT	time on treatment
TTBR	time to best response
TTR	time to response
ULN	upper limit of normal

Version history

Table JZJA.1.1. SAP Version History Summary

SAP Version	Approval Date	Change	Rationale
1	07 August 2019	Not Applicable	Original version
2	07 May 20021	Define analysis and analysis set for the Japan regulatory submission	Before the data cutoff for the Japan regulatory submission
3	See date on Page 1	Define analysis and analysis set for the final clinical study report	To define the analysis set for the final clinical study report

1. Introduction

The purpose of this SAP is to define the analysis set for the final clinical study report of J2G-OX-JZJA (JZJA) and document the statistical methods to be used to demonstrate the effectiveness and the safety of selpercatinib in patients with *RET* advanced solid tumors, including *RET* fusion-positive NSCLC, thyroid, medullary thyroid cancer, and other tumors with *RET* activation.

1.1. Objectives and Endpoints

Objectives	Endpoints
Primary	
• Assess the antitumor activity of selpercatinib in patients with Advanced Solid Tumors, including *RET* fusion-positive solid tumors, medullary thyroid cancer, and other tumors with *RET* activation	• ORR based on IRC assessment using RECIST 1.1
Secondary	
• Assess the antitumor activity of selpercatinib in patients with Advanced Solid Tumors, including RET fusion-positive solid tumors, medullary thyroid cancer, and other tumors with RET activation	• ORR based on investigator assessment using RECIST 1.1 • CNS ORR (by IRC; patients with RET fusion NSCLC and brain metastases) • CNS DOR (by IRC; patients with RET fusion NSCLC and brain metastases) • Biochemical response • TTR (by IRC and investigator) • TTBR (by IRC and investigator) • DOR (by IRC and investigator) • CBR (by IRC and investigator) • PFS (by IRC and investigator) • OS
• Determine the safety profile and tolerability of selpercatinib in patients with Advanced Solid Tumors, including *RET* fusion-positive solid tumors, medullary thyroid cancer, and other tumors with *RET* activation	• Safety per CTCAE (including but not limited to): frequency and severity of TEAEs, SAEs, deaths, and clinical laboratory abnormalities • Changes in haematology and blood chemistry values • Assessments of physical examinations • Vital signs, and • ECGs
• To characterize the PK properties of selpercatinib	• Plasma concentrations of selpercatinib and PK parameters, including, but not limited to, AUC_{0-24}, C_{max}, and T_{max}

Abbreviations: AUC_{0-24} = area under the plasma concentration-time curve from 0 to 24 hours; C_{max} = maximum observed drug concentration; CTCAE = Common Terminology Criteria for Adverse Events; CBR = clinical benefit rate; CNS = central nervous system; DOR = duration of response; ECGs = electrocardiograms; IRC = independent review committee; NSCLC = non-small cell lung cancer; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetic; RECIST = Response Evaluation Criteria in Solid Tumors; *RET* = Rearranged during Transfection ; SAE = severe adverse event; TEAE = treatment-emergent adverse event; T_{max} = time to maximum plasma; TTBR = time to best response; TTR = time to response.

1.2. Study Design

This is an open-label, multicenter, Phase 1/2 study in patients with advanced solid tumors, including *RET* fusion–positive solid tumors (for example, NSCLC and thyroid), *RET*-mutant MTC, and other tumors with *RET* activation (for example, mutations in other tumor types or

other evidence of *RET* activation). This study includes 2 parts: Phase 1 (dose escalation and dose expansion) and Phase 2.

A detailed description of the study design is contained in the protocol.

2. Analysis Sets

For the purposes of ana*lysis, the following analysis sets are defined.*

2.1. Safety Analysis Set

Table JZJA.2.1 provides an overview of the safety analysis set.

Table JZJA.2.1. Description of Safety Analysis Sets

Safety Analysis Set	Analysis Set Description
Overall Safety Analysis Set	All patients who received at least 1 or more doses of selpercatinib regardless of diagnosis or line of therapy
RET fusion-positive NSCLC safety analysis set	All patients with *RET* fusion-positive NSCLC who received at least 1 dose of selpercatinib. This is a subset of the Overall Safety Population.
RET mutant MTC safety analysis set	All patients with *RET* mutant MTC who received at least 1 dose of selpercatinib. This is a subset of the Overall Safety Population.
RET fusion-positive thyroid safety analysis set	All patients with *RET* fusion-positive thyroid who received at least 1 dose of selpercatinib. This is a subset of the Overall Safety Population.
RET mutant non-MTC safety analysis set [a]	All patients with *RET* mutant non-MTC who received at least 1 dose of selpercatinib. This is a subset of the Overall Safety Population.
Prior *RET* inhibitor safety analysis set [a]	All patients who have received prior treatment with a selective *RET* inhibitor. This is a subset of the Overall Safety Population. This group includes patients with *RET* fusion-positive NSCLC, *RET* fusion-positive Thyroid and *RET* mutant MTC.

Abbreviations: MTC = medullary thyroid cancer; NSCLC = non-small cell lung cancer; *RET* = Rearranged during Transfection.

[a] Selected safety analyses will be performed.

As of the data cutoff, enrollment is still ongoing for *RET* fusion-positive cancer other than NSCLC and thyroid cancer and the safety analysis and efficacy analysis on the population will be included in the respective CSR.

2.2. Efficacy Analysis Set

Patients who received at least 1 dose of selpercatinib and achieved at least 6 months of potential follow-up time from the first dose of selpercatinib (or disease progression or death, whichever occurred first), as of a data cutoff, will be considered eligible for efficacy analyses. The efficacy analysis sets are defined by tumor diagnosis and line of therapy and described in Table JZJA.2.2.

Table JZJA.2.2. Description of efficacy Analysis Sets

Tumor Diagnosis/Line of Therapy	Analysis Set	Analysis Set Description
RET fusion-positive NSCLC	Patients Previously Treated with Platinum-Based Chemotherapy	Efficacy eligible patients with *RET* fusion-positive NSCLC previously treated with platinum-based chemotherapy.
	Treatment-Naïve Patients	Efficacy eligible treatment-naïve patients with *RET* fusion-positive NSCLC.

Tumor Diagnosis/Line of Therapy	Analysis Set	Analysis Set Description
	Patients Previously Treated with Other Systemic Therapy	Efficacy eligible patients with *RET* fusion-positive NSCLC previously treated with systemic therapies other than platinum-based chemotherapy.
	Patients with Non-measurable disease	Efficacy eligible patients with *RET* fusion-positive NSCLC previously treated and treatment-naïve patients without measurable disease by RECIST v1.1.
	CNS Response Analysis Set	Efficacy eligible patients with *RET* fusion-positive NSCLC who had investigator-identified CNS metastases at baseline (reported as target or nontarget lesion per RECIST v1.1).
RET mutant MTC	Patients Not Previously Treated with Cabozantinib and/or Vandetinib	Efficacy eligible patients with *RET*-mutant MTC that have had no prior systemic therapy or have been treated with a prior systemic therapy besides cabozantinib and vandetanib.
	Patients Previously Treated with Cabozantinib and/or Vandetinib	Efficacy eligible patients with *RET*-mutant MTC treated with cabozantinib and/or vandetanib.
	Patients with Non-Measurable Disease	Efficacy eligible patients with *RET*-mutant MTC previously treated and treatment naïve patients without measurable disease by RECIST v1.1
	Patients Naïve to Any Systemic Therapy	This analysis set is a subset of the 'Patients Not Previously Treated with Cabozatibnib and/or Vandetanib' analysis set
	Patients Naïve to Cabozantinib and Vandetinib But Previously Treated with Other Systemic Therapy	This analysis set is a subset of the 'Patients Not Previously Treated with Cabozatibnib and/or Vandetanib' analysis set
RET fusion-positive thyroid	Patients Not Previously Treated with systemic therapy other than RAI	Efficacy eligible patients with *RET* fusion-positive TC that have had no prior systemic therapy (lenvatinib, sorafenib) other than RAI
	Patients Previously Treated with systemic therapy other than RAI	Efficacy eligible patients with *RET* fusion-positive TC previously treated with systemic therapy (lenvatinib, sorafenib) other than RAI
RET mutant non-MTC [a]	Patients with *RET* mutant non-MTC	Efficacy eligible patients with *RET* mutant non-MTC
Prior *RET* inhibitor [a,b]	Patients who have received prior treatment with a selective *RET* inhibitor	Efficacy eligible patients with a prior selective *RET* inhibitor

Abbreviations: CNS = central nervous system; MTC = medullary thyroid cancer; NSCLC = non-small cell lung cancer; RAI = radioactive iodine; RECIST = Response Evaluation Criteria in Solid Tumours; *RET* = Rearranged during Transfection; TC = thyroid cancer.

[a] Selected efficacy analysis will be performed.

[b] This group includes patients with *RET* fusion NSCLC, *RET* fusion thyroid, and *RET* mutant MTC and is excluded from the other efficacy analysis sets.

3. Data Cutoff

A data cutoff date will be announced when prespecified requirement in population of patients with *RET* fusion-positive thyroid is met.

Among at least 50 *RET* fusion-positive thyroid cancer who have received radioactive iodine (if appropriate for their tumor histology), all responding patients have been followed for 12 months following onset of response by investigator assessment or until disease progression, whichever comes first.

4. Statistical Analyses

4.1. General Considerations

Statistical analysis of this study will be the responsibility of Eli Lilly and Company (Lilly) or its designee. All tests of treatment effects will be conducted at a 2-sided alpha level of 0.05, unless otherwise stated, and 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, number of participants, mean, median, standard deviation, minimum, and maximum). Categorical variables will be summarized by frequency and its corresponding percentage.

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

4.1.1. Definitions

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

- baseline: baseline is defined as the last value recorded for a variable prior to the patient receiving the first dose of selpercatinib
- common conventions:
    - 1 pound = 0.454 kg
    - 1 inch = 2.54 cm
    - 1 year = 365.25 days. Year is calculated as (days/365.25) and will be rounded up to 1 significant digit for purposes of presentation
    - 1 month = 30.4375 days. Month is calculated as (days/30.4375) and will be rounded up to 1 significant digit for purposes of presentation
    - dates, time, and date/time fields will be displayed in data listings in ISO 8601 formats
    - change from baseline = test value at Visit X – baseline value, and
    - percentage change from baseline = 100 × (test value at Visit X – baseline value) / baseline value
- Study day: Study day is calculated as assessment date/event 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/event – first dose date.

4.1.2. Handling of Dropouts or Missing Data

4.1.2.1. Missing Data

For data summarized over time by visit, no imputations will be performed on missing data. All analyses will be based on observed data only. The effective sample sizes at each assessment visit

will be based on the total number of patients with nonmissing data for the parameter of interest at that visit.

Missing or partially missing dates for initial disease diagnosis will be imputed. If the month and year of the diagnosis are provided but the day is missing, the missing day is imputed as 15. If only the year is provided, then the missing month and day are imputed as July 1 for the calculation.

4.1.2.2. Unscheduled Visits

In general, for by-visit summaries, data will be presented based on the visit number and corresponding visit name (that is, name of planned clinical encounter). Visit windowing will not be used for handling unscheduled visits. Instead, all unscheduled visits will be assigned a visit name of "Unscheduled." Such visits will be included in all by-visit summaries and data listing and will contribute to the derivation of best- or worst-case values when required.

The visit number for unscheduled visits will be assigned by adding 0.01 to the visit number of the previously scheduled visit to facilitate chronological sorting. As an illustration, if an unscheduled visit occurs after Study Date 1, where the visit number is "1," the unscheduled visit will have visit number of "1.01."

4.2. Participant Dispositions

A detailed description of participant disposition will be provided, according to Consolidated Standards of Reporting Trials publishing requirements, including a summary of the number and percentage of participants entered the study, enrolled in the study, and treated, as well as number and percentage of participants completing the study or discontinuing prior to study completion (overall and by reason for discontinuation).

The disposition of patients will be summarized by tabulating the number and percentage of patients as of a data cutoff date:

- treatment disposition
    - starting dose of selpercatinib and frequency of administration
    - continuing to receive selpercatinib, and
    - permanently discontinued selpercatinib and the primary reason
- study disposition
    - patients who discontinued from study and the primary reason, and
    - time on study.

Patients with PD may be allowed to continue study drug if, in the opinion of the investigator, the patient is deriving clinical benefit from continuing study treatment, and continuation of treatment is approved by the sponsor. The number and percentage of such patients continuing to receive study drug after the documentation of disease progression will be presented.

4.3. Primary Endpoint Analysis

The primary endpoint is ORR based on RECIST version 1.1 by IRC.

4.3.1. Definition of Endpoint

BOR for each patient (CR, PR, SD, PD, or inevaluable) occurring between the first dose of selpercatinib and the date of documented disease progression or the date of subsequent anticancer therapy or cancer-related surgery will be determined based on the RECIST 1.1. All objective responses will be confirmed by a second scan at least 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 may be used to depict graphically the maximum decrease from baseline in the sum of the diameters of target lesions.

The estimate of ORR will be calculated based on the maximum likelihood estimator (that is, crude proportion of patients with BOR of CR or PR). The estimate of the ORR will be accompanied by 2-sided 95% exact binomial CI.

4.3.2. ORR by Investigator Assessment

Best overall response for each patient based on the RECIST 1.1 by investigator assessment will be analyzed as a secondary endpoint analysis. ORR by investigator will be analyzed in the same manner as ORR by IRC.

To evaluate agreement between IRC and investigator assessments, 2×2 contingency table will be prepared. Correspondence rate and its 2-sided 95% exact binomial CI will be estimated.

4.3.3. Duration of Response

DOR will be calculated for patients with CR or PR as their best overall response. 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 recurrent or disease progression 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.

DOR will be right censored for patients who meet one or more of the following conditions:

- subsequent anticancer therapy or cancer-related surgery in the absence of documented disease progression
- died or experienced documented disease progression after missing 2 or more consecutively scheduled disease assessment visits
- alive and without documented disease progression on or before the data cutoff date, and
- discontinue treatment and loss to follow up.

If a patient meets more than one of these conditions, then the scenario that occurs first will be used for the analysis. The event or censoring date will be determined based on the conventions listed in Table JZLA.4.1.

Table JZLA.4.1. DOR Censoring Scheme

Situation	Date of Event or Censoring	Outcome
Death or disease progression between planned disease assessments	Date of death or first disease assessment showing disease progression, whichever occurs first	Event
Subsequent anticancer treatment started before disease progression or death (without disease progression beforehand)	Date of last evaluable disease assessment prior to start of subsequent anticancer treatment	Censored
Death or disease progression after missing 2 or more consecutively scheduled disease assessments	Date of last evaluable disease assessment visit without documentation of disease progression before the first missed visit	Censored
Alive and without disease progression	Date of last evaluable disease assessment	Censored
Discontinue treatment and loss to follow up	Date of last evaluable disease assessment	Censored

Abbreviation: DOR = duration of response.

The patient's overall response status as of the date cutoff date will be summarized by tabulating the number and percentage of patients with confirmed CR or PR as follows:

- response continuing
- subsequent anticancer therapy/cancer-related surgery without documented disease progression beforehand
- discontinued treatment and loss to follow up
- documented disease progression, and
- died (for patients who did not have documented disease progression beforehand).

DOR will be summarized descriptively using the Kaplan-Meier method (Kaplan and Meier 1958). 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 DOR will be estimated according to the reverse Kaplan-Meier estimate of potential follow-up (Schemper and Smith 1996).

4.3.4. CNS ORR and CNS DOR

The CNS ORR and CNS DOR will be assessed by IRC only according to the IRC charter and will be analyzed using the same method described above for the analyses of ORR and DOR.

4.3.5. Biochemical Response

The best biochemical response (Wells 2012) for both calcitonin and CEA is defined for MTC patients as follows:

- CR: normalization of serum levels following treatment maintained for a minimum of 4 weeks
- PR: ≥50% decrease from baseline levels maintained for a minimum of 4 weeks
- stable: between +50% and –50% change from baseline levels maintained for a minimum of 4 weeks
- progression: ≥50% increase from baseline maintained for a minimum of 4 weeks, and
- NE: if a patient does not meet the definition of any outcome described above.

The best biochemical responses for CEA and calcitonin will be derived programmatically based on the baseline and postbaseline values according to the definitions described above.

The biochemical response rate of calcitonin or CEA is defined as the proportion of patients with a best biochemical response of CR or PR.

The point estimate of the biochemical response rate and the 2-sided 95% exact binomial CI will be presented for calcitonin and for CEA. The best biochemical response for calcitonin or CEA will be summarized descriptively to show the number and percentage of patients in each response category.

Waterfall plots will be used to depict graphically the best change of calcitonin and CEA for each patient

4.3.6. Time to Response

TTR is defined as the number of months elapsed between the date of the first dose of selpercatinib and the first documentation of objective response (CR or PR, whichever occurs earlier) that is subsequently confirmed. TTR will be calculated as follows for patients who have a BOR of confirmed CR or confirmed PR:

$$\text{TTR (months)} = (\text{Response Start Date} - \text{First Dose Date} + 1) / 30.4375$$

4.3.7. Time to Best Response

TTBR is defined as the number of months elapsed between the date of the first dose of selpercatinib and the first documentation of CR (if patient's BOR is confirmed CR) or PR (if patient's BOR is confirmed PR) that is subsequently confirmed. TTBR will be calculated as follows for patients who have a BOR of confirmed CR or confirmed PR:

$$\text{TTBR (months)} = (\text{Best Response Start Date} - \text{First Dose Date} + 1) / 30.4375$$

TTBR will be summarized descriptively in the same manner as TTR.

4.3.8. Clinical Benefit Rate

CBR will be calculated based on the proportion of patients with BOR confirmed CR, PR, or SD lasting 16 or more weeks. CBR will be measured from the date of the first dose selpercatinib until the criteria for disease progression are first met. The analysis of CBR will be based on the methods described for ORR and will be presented in the summary table of BOR and ORR.

4.3.9. Progression-Free Survival

PFS is defined as the number of months elapsed between the date of the first dose of selpercatinib and the earliest date of documented disease progression or death (whatever the cause). Unless specified otherwise, the analytical methods described in Section 4.3.3 for DOR will be used for PFS. PFS will be calculated as follows:

PFS (months) = (Event or Censoring Date – First Dose Date + 1) / 30.4375

PFS will be right censored for patients who met one or more of the following conditions:

- no postbaseline disease assessments unless death occurred prior to the first planned assessment (in which case death will be considered a PFS event)
- subsequent anticancer therapy or cancer-related surgery in the absence of documented disease progression
- died or documented disease progression after missing 2 or more consecutively scheduled disease assessment visits
- alive and without documented disease progression on or before the data cutoff date, and
- discontinue treatment and loss to follow up.

If a patient meets more than one of these conditions, then the scenario that occurs first will be used for analysis. The event or censoring date will be determined based on the conventions listed in Table JZLA.4.2.

Table JZLA.4.2. PFS Censoring Scheme

Situation	Date of Event or Censoring	Outcome
Death before first planned disease assessment	Date of death	Event
Death or disease progression between planned disease assessments	Date of death or first disease assessment showing disease progression, whichever occurs first	Event
No postbaseline disease assessments	Date of first dose of selpercatinib	Censored
Subsequent anticancer treatment started before disease progression or death (without disease progression beforehand)	Date of last evaluable disease assessment prior to start of subsequent anticancer treatment	Censored
Death or disease progression after missing 2 or more consecutively scheduled disease assessments	Date of last evaluable disease assessment visit without documentation of disease progression before the first missed visit	Censored
Alive and without disease progression	Date of last evaluable disease assessment	Censored
Discontinue treatment and loss to follow up	Date of last evaluable disease assessment	Censored

Abbreviation: PFS = progression-free survival.

4.3.10. Overall Survival

OS is defined as the number of months elapsed between the date of the first dose of selpercatinib and the date of death (whatever the cause). Patients who are alive or lost to follow-up as of the data cutoff date will be right-censored. The censoring date will be determined from the date the

patient was last known to be alive. Based on these considerations, OS will be calculated as follows:

OS (months) = (Death or Censoring Date – First Dose Date + 1) / 30.4375

The duration of OS will be summarized descriptively using the Kaplan-Meier method with the 95% CI about the median calculated using Greenwood's formula. Median follow-up for OS will be estimated according to the reverse Kaplan-Meier estimate of potential follow-up (Schemper and Smith 1996).

4.3.11. Safety Analyses

4.3.11.1. General Considerations

This section describes the statistical methods to be used for analyses intended to demonstrate the safety and tolerability of selpercatinib.

Safety will be assessed based on the incidence and severity of all AEs and SAEs. Changes in clinical laboratory tests, vital signs, body weight, performance status, and 12-lead ECGs also will be assessed. These data presentations will be performed for the safety analysis set as specified in Section 2.

4.3.11.2. Adverse Events

Summary tables will be provided for all reported treatment-emergent AEs and treatment-emergent SAEs, defined respectively, as AEs and SAEs that started on or after the date of the first dose of selpercatinib (Study Day 1). For cases in which it is not possible to ascertain treatment-emergence, the event will be classified as treatment-emergent.

The reported AE term will be coded using version 21.0 of the MedDRA. The severity of each AE will be graded by the Investigator based on version 4.03 of the National Cancer Institute CTCAE. If a severity grading scale does not exist for an AE, the investigator will classify the severity as mild, moderate, severe, life-threatening/debilitating, or fatal based on the criteria described in study protocol. The causal relationship between the occurrence of an AE and study drug will be judged by the Investigator as "related" or "not related."

AEs will be summarized based on the number and percentage of patients experiencing events by MedDRA system organ class and preferred term. If a patient experiences repeated episodes of the same AE (as defined by the MedDRA system organ class and preferred term), the event with the highest reported severity grade and the strongest causal relationship to study drug will be used for purposes of the incidence tabulations.

Tabular summaries will be provided for treatment-emergent AEs and SAEs:

- all AEs
- by maximum severity grade
- by relationship to study drug
- AEs with action of study drug withheld or dosage modified

- AEs with action of study drug permanently discontinued
- SAEs

Narratives will be prepared for all patients who meet one or more of the following conditions:

- death while on treatment or within 28 days of the last dose irrespective of cause
- treatment-emergent SAEs
- AE with action taken of study drug permanently discontinued

4.3.11.3. Deaths

Death information is reported in the study exit case report form for all deaths. Incidences of deaths are to be reported, along with the primary cause of death in a summary table. All deaths including on-study death (deaths that occurred within 28 days of treatment discontinuation) will be presented in a patient listing, which will supplement the narratives and will include the primary cause of death, cumulative duration of treatment, and the number of days between the date of the last dose of study drug and death.

4.3.11.4. Laboratory Values

Blood samples for the following clinical laboratory tests were collected and analyzed for safety:

- Hematology: hemoglobin, hematocrit, platelet count, red blood cell count, and white blood cell count with differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils)
- Serum chemistries (non-fasting): ALT, AST, blood urea nitrogen, total cholesterol, creatinine, glucose, lactate dehydrogenase, total and direct bilirubin, total protein, sodium, potassium, calcium, chloride, bicarbonate, magnesium, phosphate, and urea
- Thyroid panel: thyroid-stimulating hormone, free triiodothyronine, and free thyroxine

Clinical laboratory samples were processed at the clinical site or at an affiliated local laboratory facility. For purposes of analysis and reporting, laboratory values will be standardized using International System of Units or clinically appropriate units. For laboratory values that are reported using a nonnumeric qualifier (for example, less than [<] signs or greater than [>] signs), the reported numeric value will be used for analysis without the qualifier.

4.4.8.4.1 Incidence of Laboratory Abnormalities

Whenever defined, laboratory values will be assigned toxicity grades based on version 4.03 of the CTCAE. For some laboratory tests, these criteria may include qualifying definitions (for example, clinical AE and/or requirement for concomitant medication) in addition to the specific laboratory value used for the definition of the toxicity grades. For such tests, the qualifying definitions will not be used for the assignment of toxicity grades. Generic normal ranges may be applied whenever the percentage of missing reference range is not negligible.

The “worst” change (minimum and/or maximum) in each laboratory value occurring during treatment will be assessed by means of shift tables showing the number and proportion of patients with directional shifts in CTCAE toxicity grades relative to the baseline grade. For laboratory variables without CTCAE toxicity grades (such as thyroid function), similar tables

will be constructed showing shifts to outside (above or below) the local laboratory normal range relative to baseline.

4.4.8.4.2 Changes in Laboratory Values from Baseline

Hematology, serum chemistry, and thyroid function values will be summarized in a descriptive manner by calculating the mean, standard deviation, median, and range of the following values that are derived for each patient:

- baseline value
- minimum postbaseline value and corresponding change from baseline
- maximum postbaseline value and corresponding change from baseline
- last postbaseline value and corresponding change from baseline

The baseline value will be determined using the convention described in Section 4.1.1. In addition, incidence of the most extreme treatment-emergent postbaseline abnormal laboratory parameters will be summarized. The treatment-emergent laboratory abnormality is defined as a laboratory value at least 1 toxicity grade higher than the baseline grade.

4.4. Exploratory Endpoint Analysis

4.4.1. Disease Control Rate

DCR will be calculated based on the proportion of patients with best overall response confirmed CR, PR, or SD. DCR will be measured from the date of the first dose selpercatinib until the criteria for disease progression are first met. The analysis of DCR will be based on the methods described for ORR and will be presented in the summary table of best overall response and ORR.

4.4.2. Intra-patient Analysis

Prior therapy data will be used to perform an exploratory analysis comparing benefit achieved on the last therapy patients received prior to the study enrollment to benefit achieved on selpercatinib treatment using each study patient as their own control. A known limitation of this analysis is retrospective prior therapy data collection based on patients' medical records without central review and confirmation based on RECIST criteria.

4.5. Other Safety Analyses

4.5.1. Vital Signs

The following vital signs were measured 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)

Each of these vital signs will be summarized in a descriptive manner by calculating the mean, standard deviation, median, and range of the following values that are derived for each patient:

- baseline value
- minimum postbaseline value and corresponding change from baseline
- maximum postbaseline value and corresponding change from baseline
- last postbaseline value and corresponding change from baseline

The baseline value will be determined using the convention described in Section 4.1.1.

4.5.2. Body Weight

Body weight was measured at screening and at periodic time points following the initiation of selpercatinib. Changes in body weight will be summarized in a descriptive manner based on the conventions for postbaseline changes in laboratory values.

4.5.3. Performance Status

Performance status is graded according to either the ECOG, or Lansky scales depending upon the patient's age and tumor type. Data from the Lansky scales will be mapped to the ECOG performance scale (0–5) to maximize uniformity. Shift table analysis of baseline vs worst on-treatment score will be presented.

4.5.4. Adverse Events of Special Interest

Based upon information available to date and/or known class effects of this compound, several categories of AE have been designated to be of special interest. These include the following which are discussed below:

- liver injury
- hypersensitivity
- hypertension
- QT prolongation

The latest list of adverse events of special interest will be included in the program level safety analysis plan. As the understanding of the safety of selpercatinib increases, the list will be modified as needed.

Liver function tests will be presented using conventional summary statistics, toxicity shift table analysis, and by time-to-event plots. Possible drug-induced liver injury will be assessed as defined in FDA guidance (FDA 2009). Hy's Law cases of drug-induced liver injury have the following components:

- The drug causes hepatocellular injury as evidenced by an elevation of ALT or AST to 3-fold or greater of the ULN relative to control (or in this context to baseline levels).
- In addition to the transaminase increases, an associated (that is, concomitant) elevation of total serum bilirubin to 2-fold or greater of the ULN without initial findings of cholestasis (elevated alkaline phosphatase) was found.
- No other explanation can be found for the combination of increased transaminase(s) and total bilirubin, such as viral hepatitis, preexisting acute liver disease, or concomitant drug capable of causing the observed injury.

Narratives will be prepared for patients who meet all criteria for Hy's Law; these will include medical history, description of the event, action taken (including study drug action), and outcome.

4.5.5. Electrocardiograms

The 12-lead ECGs were performed at screening and at periodic time points throughout selpercatinib treatment. An ECG assessment was also done at the safety follow-up visit if treatment-emergent abnormalities were found at the end-of-treatment visit.

The following ECG parameters and clinical findings were collected:

- Heart rate (beats per minute)
- PR interval (milliseconds)
- R wave-to-R wave (RR) interval (milliseconds)
- QRS interval (milliseconds)
- QT interval (milliseconds)
- QTcF interval (milliseconds)

If QTcF is not reported, Frederica's correction to the reported QT interval will be derived (in milliseconds) for all patients and time points as follows:

$$\text{QTcF (ms)} = \frac{QT\ (ms)}{\sqrt[3]{RR\ (ms)/1000}}$$

If the R wave-to-R wave (RR) interval is not reported, it will be derived from the reported heart rate (HR) as follows for the derivation of RR:

$$\text{RR (ms)} = 1000 * \frac{60}{HR\ (bpm)}$$

All components for these calculations must be taken from the same assessment, which will be identified in the database by the date-time of the ECG recording.

The mean of the replicate ECG measurements will be used for the analysis whenever replicates are reported for a patient and time point (scheduled or unscheduled).

Each ECG parameter will be summarized in a descriptive manner by calculating the mean, standard deviation, median, and range of the following values that are derived for each patient:

- baseline value
- minimum postbaseline value and corresponding change
- maximum postbaseline value and
- last postbaseline value

Categorical analyses of the QTcF interval data across time points will be performed using shifts from baseline for the number and percentage of patients meeting or exceeding the following threshold values:

4.5.6. Extent of Exposure

Exposure to selpercatinib will be summarized based on the following:

- time on treatment
- dose intensities
- dosage modifications

4.5.6.1. Time on Treatment

TOT will be summarized descriptively. For patients who permanently discontinued selpercatinib as of the data cutoff date, TOT will be calculated as follows:

TOT (months) = (Last Dose Date – First Dose Date + 1) / 30.4375

The last dose date reported on the End of Treatment case report form will be used. For patients continuing to receive selpercatinib as of the data cutoff date, TOT will be calculated as follows:

TOT (months) = (Data cutoff Date – First Dose Date + 1) / 30.4375

4.5.6.2. Dose Intensities

Selpercatinib dose intensities will be summarized descriptively as ADI, PDI, and RDI.

- The ADI of selpercatinib (mg/day) will be calculated as the actual cumulative dose of LOXO-292 (mg) received divided by TOT (days).
- The PDI of selpercatinib (mg/day) will be as follows:
  - For once daily dosing schedule, the PDI (mg/day) = assigned dose level (mg)/day
  - For BID dosing schedule, the PDI (mg/day) = assigned dose level (mg) x 2/day
  - PDI will be calculated taking into account the starting dose and the escalated dose if applicable
- The RDI is the percentage of dose received relative to the planned dose through to treatment discontinuation and is defined as follows:

RDI (%) = (ADI / PDI) * 100%

4.5.6.3. Dose Modifications

The number and percentage of patients with dose reductions, dose withheld, and dose increases will be tabulated with the reason for each dose modification.

4.6. Other Analyses

4.6.1. Subgroup analyses

Supportive analyses will be performed to assess the safety and tolerability of selpercatinib across selected subgroups and special populations. These analyses will be conducted using the Safety Analysis Set. The incidence of treatment-emergent AEs and SAEs will be calculated for the subgroups and special populations defined by the following:

- age at enrollment (<65 years, ≥65 years)

- sex (male, female)
- race (White, other)

Depending upon the requests or requirements of individual regulatory authorities, age groupings other than those specified above may be utilized for supplemental analyses. The decision to combine selected categories and the manner in which they may be combined will be deferred until the analysis.

4.7. Changes to Protocol-Planned Analyses

Efficacy analyses will be performed by proposed indication instead of protocol-defined cohorts.

5. Supporting Documentation

5.1. Appendix 1: Demographic and Baseline Characteristics

Baseline characteristics of patients included in the safety analysis set will be summarized in a tabular manner for the following factors:

- demography
- cancer and other relevant medical history
- prior cancer treatments
- *RET* alteration

5.1.1. Demography

The following variables will be summarized across patients to describe the demographics and other characteristics at enrollment:

- Age at enrollment - summarized as a continuous variable in years relative to the date informed consent is signed. Age will also be summarized categorically based on the following age groups:
  - <18 years
  - 18 to <45 years
  - 45 to <65 years
  - 65 to <75 years
  - ≥75 years
- sex (male, female)
- race (White, Black, Asian, other)
- ethnicity (Hispanic or Latino, not Hispanic or Latino, declines to state)
- height (cm)
- weight (kg)
- body mass index
- performance status – will be presented using the ECOG scale; data collected using the Lansky scale will be mapped to ECOG using published methods

5.1.2. Cancer History

The following variables will be summarized across patients to describe the types of cancers:

- primary cancer diagnosis (standardized term)
- stage of disease at initial diagnosis (I–IV)
- time since initial diagnosis (years)
- metastatic disease at enrollment (yes, no)
- time since initial diagnosis of metastatic disease (years)

5.1.3. Prior Cancer Treatment

The following variables will be summarized across patients to characterize the extent of prior cancer treatments:

- prior radiotherapy (yes, no)
- prior cancer-related surgery (yes, no)
- prior systemic treatments (yes, no)
- number of prior systemic regimens or treatment courses (0, 1, 2, ≥3)
- number of prior systemic regimens or treatment courses (as a continuous variable)
- BOR and discontinuation of the last therapy prior to enrollment

Prior systemic cancer therapies will be assigned standardized terms by the medical monitor.

5.1.4. RET Alteration Status

The *Ret* fusion partner will be summarized.

5.1.5. Noncancer Medical History

Noncancer medical history will be displayed in patient listing format.

5.2. Appendix 2: Protocol Deviation

Protocol deviations will be identified and reported by the process described in the current version of the study Protocol Deviation Plan. The number and percentage of patients with reported protocol deviations will be tabulated by category. Protocol deviations will be listed by patient.

6. References

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