Official Title: A Phase 1/2 Study of the Highly-Selective RET Inhibitor, BLU-667, in Patients with Thyroid Cancer, Non−Small Cell Lung Cancer (NSCLC) and Other Advanced Solid Tumors

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STATISTICAL ANALYSIS PLAN

STUDY TITLE: A PHASE 1/2 STUDY OF THE HIGHLY-SELECTIVE RET INHIBITOR, BLU-667, IN PATIENTS WITH THYROID CANCER, NON-SMALL CELL LUNG CANCER (NSCLC) AND OTHER ADVANCED SOLID TUMORS

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STATISTICAL ANALYSIS PLAN APPROVAL

SPONSOR:	F. Hoffmann-La Roche Ltd
LEGAL REGISTERED ADDRESS:	Grenzacherstrasse 124 4070 Basel, Switzerland
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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Term	Description
AE	adverse event
ANCOVA	analysis of covariance
BGPL	Biometrics Global Process Library
BMI	body mass index
CSR	Clinical Study Report
DMC	Data Monitoring Committee
HR	hazard ratio
IA	interim analysis
ICH	International Council on Harmonization
iDMC	independent Data Monitoring Committee
IMC	Internal Monitoring Committee
IRF	Independent Review Facility
ITT	intent to treat
IxRx	interactive voice/web-based response system
LLoQ	lower limit of quantification
MDD	minimally detectable difference
MedDRA	Medical Dictionary for Regulatory Activities
NMPA	National Medical Products Administration
OS	overall survival
PFS	progression-free survival
PRO	patient-reported outcomes
PD	Pharmacodynamics
PK	Pharmacokinetic
SAE	serious adverse events
SAP	Statistical Analysis Plan
SMART	sequential multiple assignment randomized study
SMQs	standardized MedDRA queries

1. INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to describe the planned analysis and data reporting for protocol BO42863 (BLU-667-1101/ARROW, hereafter referred to as BO42863) "A Phase 1/2 Study of the Highly-selective RET Inhibitor, BLU-667, in Patients with Thyroid Cancer, Non-Small Cell Lung Cancer (NSCLC) and Other Advanced Solid Tumors" for the completion of the Clinical Study Report (CSR) to support new drug application (NDA) filing of pralsetinib (BLU-667) for 1) Rearranged during transfection (RET)-fusion positive NSCLC patients, 2) RET-mutation positive medullary thyroid cancer (MTC) patients and RET-fusion positive thyroid cancer patients, 3) RET-fusion other solid tumor, and other specific types, respectively. Herein, RET-fusion NSCLC refers to RET-fusion positive NSCLC patients, RET-mutation MTC patients refers to RET-mutation positive MTC, and RET-fusion thyroid cancer patients refers to RET-fusion positive thyroid cancer patients, RET-fusion other solid tumors refer to RET-fusion other solid tumors, respectively.

This SAP is based on global Protocol Amendment 14 (PA14) (Dated, 28 March 2022).

Any additional post-hoc analysis performed in submission documents but not described in this version of SAP will be clearly documented in the corresponding documents for 1) RET-fusion NSCLC NDA, 2) RET-mutation MTC and RET-fusion thyroid cancer, 3) RET-fusion other solid tumors, and other specific types, respectively.

Pharmacokinetic (PK) analysis, including PK profile of pralsetinib and correlated drug exposure, and analyses of patients who undergo continuous Holter monitoring are not within the scope of this SAP and will be addressed in separate document or report. Therefore, the PK Population and electrocardiogram (ECG) Population specified in the protocol will not be included in this SAP.

The planned analyses related to the Dose-Determining Population, which have been described in SAP Version 2.0 used for NDA filing of pralsetinib for RET-fusion positive NSCLC patients, will not be included in this version. Similarly, the planned analyses related to the dose escalation patients (Phase 1 patients) of Safety Population, which have been described in SAP Version 2.0, will not be repeated in this version unless modifications are needed.

The planned analyses related to the mitogen-activated protein kinases pathway expression signature, which have been also described in SAP Version 2.0, will not be included in this version.

1.1 STUDY DESIGN

This is a Phase 1/2, open-label, first-in-human (FIH) study designed to evaluate the safety, tolerability, PK, pharmacodynamics, and preliminary antineoplastic activity of pralsetinib, a potent and selective RET inhibitor, administered orally in patients with

medullary thyroid cancer (MTC), RET-altered NSCLC, and other RET-altered solid tumors.

The study consists of 2 parts, a dose-escalation part (Phase 1) and an expansion part (Phase 2) (Figure 1). Both parts will enroll patients with RET-altered advanced non-resectable NSCLC, advanced non-resectable thyroid cancer and other advanced non-resectable solid tumors that have experienced progression following standard systemic therapy; have not adequately responded to or are intolerant to standard systemic therapy; for whom the Investigator has determined that the treatment with standard therapy is not appropriate; or for whom there is no acceptable standard therapy for their disease. Additionally, the Phase 2 dose expansion part of the study allows for treatment naïve patients with RET-fusion positive metastatic NSCLC and advanced MTC to be enrolled and treated.

The dose-escalation portion of the study (Phase 1) enrollment was completed on 3 April 2018. It employed the Bayesian optimal interval (BOIN) design to find the maximum tolerated dose (MTD) of pralsetinib. Dose escalation continued to enroll in cohorts of 3-6 (1-3 for the first 3 dose levels) patients until 12 patients were treated and evaluable for dose-limiting toxicity (DLT) at one dose level, at which time the MTD or recommended Phase 2 dose (RP2D) could be determined. The total number of patients to be enrolled during the dose escalation part of the study could vary depending on the toxicity profile of pralsetinib and the number of dose levels tested prior to reaching the MTD.

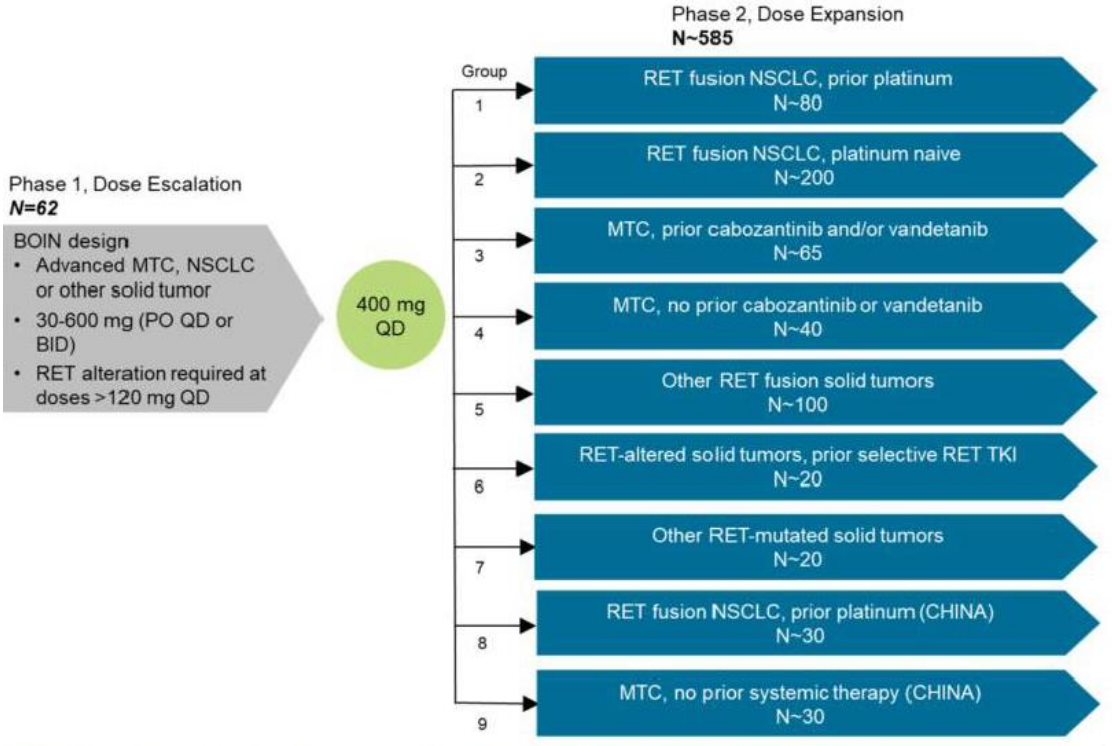
All patients treated at doses > 120 mg per day were required to have MTC, or a RET-altered solid tumor per local assessment of tumor tissue and/or blood. Additionally, these patients could be enrolled into an enrichment cohort, if it previously included less than 12 patients evaluable for dose-limiting toxicity (DLT), was reviewed at a dose-escalation meeting, and did not exceed the MTD. Data from these patients allows for further assessment of safety, PK, and pharmacodynamics.

In Phase 2, patients will enroll into 1 of 9 groups based on their tumor type and prior therapy status (if applicable).

- Group 1: NSCLC with a RET fusion previously treated with a platinum-based chemotherapy (N ~80).
- Group 2: NSCLC with a RET fusion not previously treated with a platinum-based chemotherapy, including those who have not had any systemic therapy. Prior platinum chemotherapy in the neoadjuvant and adjuvant setting is permitted if the last dose of platinum was 4 months or more before the first dose of study drug (N~200, including approximately 30 patients with prior systemic therapy).
- Group 3: MTC previously treated with cabozantinib and/or vandetanib (N ~65).
- Group 4: MTC not previously treated with cabozantinib or vandetanib (N ~40).

- Group 5: Other solid tumors with a RET fusion not eligible for any of the other groups (N ~100). Patients should have previously received standard of care (SOC) appropriate for their tumor type, unless there is no accepted standard therapy for the tumor type or the Investigator has determined that treatment with standard therapy is not appropriate. As the intent of this cohort is to enroll a variety of RET-fusion tumor types, Blueprint will notify sites if/when sufficient data are available, and accrual should cease for a particular tumor type.
- Group 6: Any solid tumors with a RET alteration (fusion or mutation) previously treated with a selective RET tyrosine kinase inhibitor (TKI) (N ~20).
- Group 7: Other solid tumors with a RET mutation previously treated with SOC appropriate for the disease type (N ~20).
- Group 8: NSCLC with a RET fusion previously treated with a platinum-based chemotherapy (China only; N ~30).
- Group 9: MTC not previously treated with systemic therapy (except prior cytotoxic chemotherapy is allowed) for advanced or metastatic disease extension cohort (China only; N ~30).

Figure 1 Study Schematic



BID=twice daily, BOIN=Bayesian optimal interval; MTC=medullary thyroid cancer; NSCLC=non–small cell lung cancer; PO=oral; QD=once daily; RET=rearranged during transfection; TKI=tyrosine kinase inhibitor.

Abbreviations: BOIN = Bayesian optimal interval; MTC = medullary thyroid cancer; NSCLC = non-small cell lung cancer; RET = rearranged during transfection; TKI = tyrosine kinase inhibitor; PO, orally; QD, once daily; BID, twice daily.

Determination of RET status, as required for enrollment of all patients except those with MTC, is based on local assessment, or central assessment if local testing is not available. All patients enrolled in Phase 2 (all 9 groups) must submit tumor tissue (archived or new) for retrospective assessment of RET status and other pathway biomarkers. Patients enrolled into Group 6 (previous treatment with a selective RET-inhibitor) are required to have a new tumor biopsy prior to enrollment.

1.2 STUDY OBJECTIVES

1.2.1 Phase 1 Objectives

1.2.1.1 Primary Objectives

- To determine the maximum tolerated dose (MTD) and recommended Phase 2 dose (RP2D) of pralsetinib.
- To determine the safety and tolerability of pralsetinib.

1.2.1.2 Secondary Objectives

- To determine the ORR by RECIST v1.1 (or Response Assessment in Neuro-Oncology [RANO], if appropriate for tumor type) for all patients treated with BLU-667 according to their disease type, and/or RET-altered status if applicable, and/or prior treatment status, if appropriate. Patients initially treated with MTD/RP2D will be pooled with Phase 2 patients.
- To assess Baseline RET gene status in plasma and/or tumor tissue and correlate with measures of antineoplastic activity including, but not limited to overall response rate (ORR), clinical benefit rate (CBR), disease control rate (DCR), and duration of response (DOR).
- To characterize the PK profile of pralsetinib and correlate drug exposure with safety assessments.
- To characterize the pharmacodynamics of pralsetinib, including, but not limited to, changes in blood calcitonin and carcinoembryonic antigen (CEA) in MTC patients only, and changes in turmor dual specificity phosphatase (DUSP6) and sprout receptor tyrosine kinase (RTK) signaling antagonist 4 (SPRY4) levels in all patients.

1.2.1.3 Exploratory Objectives

To identify potential new blood and tumor tissue biomarkers (eg, deoxyribonucleic acid [DNA], ribonucleic acid [RNA], and/or protein markers) of pharmacodynamic activity, antineoplastic activity, and/or toxicity.

1.2.2 Phase 2 Objectives

Phase 1 patients treated at the MTD/RP2D will be pooled with Phase 2 patients for Phase 2 objectives.

1.2.2.1 Primary Objectives

To determine the ORR by RECIST v1.1 (or RANO, if appropriate for tumor type) by disease type, and/or RET-altered status (including patients treated at MTD/RP2D in Phase 1), and/or prior treatment status specified in enrollment group definition, if appropriate.

To further define the safety and tolerability of pralsetinib.

1.2.2.2 Secondary Objectives

- To assess additional measures of clinical benefit including DOR, CBR, DCR, progression-free survival (PFS), and overall survival (OS) in all patients by disease type and/or RET-altered status, and/or prior treatment status explained in enrollment group definition, if appropriate. Patients treated at MTD/RP2D in Phase 1 will be pooled with Phase 2 patients for this analysis.
- To assess baseline RET gene status (ie, gene fusion partner or primary mutation and, for MTC, whether hereditary or sporadic) in plasma and/or tumor tissue and correlate with measures of antineoplastic activity including, but not limited to ORR, CBR, DOR, and DCR in all patients, including patients treated at MTD/RP2D in Phase 1, by disease type, and/or RET-altered status if applicable, and/or prior specified treatment status if appropriate.
- To characterize the pharmacokinetic (PK) profile of pralsetinib and correlate drug exposure with safety assessments, including changes in ECG intervals, and efficacy.
- To characterize the pharmacodynamics of pralsetinib, including, but not limited to, changes in blood calcitonin and carcinoembryonic antigen (CEA) in MTC patients only.
- To assess brain activity in patients with NSCLC.

1.2.2.3 Exploratory Objectives

- To identify potential new blood and tumor tissue biomarkers (eg, DNA, RNA, and/or protein markers) of pharmacodynamic activity, antineoplastic activity, and/or toxicity.
- To assess changes in quality of life (QoL) questionnaire.
- To explore disease-related symptoms, as measured by bowel movement history (MTC patients only).
- To explore clinical benefit including ORR, CBR, DCR, PFS for patients previously treated with a selective RET tyrosine kinase inhibitor.
- To assess brain activity in patients with tumor types other than NSCLC.

1.3 STUDY ENDPOINTS

1.3.1 Phase 1 Endpoints

1.3.1.1 Primary Endpoints

- MTD and RP2D of pralsetinib.

- Overall safety profile of pralsetinib, as assessed by the type, frequency, severity, timing, and relationship to study drug of any adverse events, serious adverse events, changes in vital signs, ECGs, and safety laboratory tests.

1.3.1.2 Secondary Endpoints

- ORR for all pralsetinib treated patients according to patients' disease type and/or RET-altered status if applicable, and/or prior treatment status if appropriate. Patients initially treated with MTD/RP2D in Phase 1 will be pooled with Phase 2 patients accordingly.
- RET gene status and correlation between RET gene status and ORR, CBR, DOR, and DCR, and other measures of antineoplastic activity (in plasma and/or tissue) in all patients according to their disease type and/or RET-altered status, if applicable, and/or prior treatment status, if appropriate.
- PK parameters of pralsetinib: Pharmacokinetic parameters of interest will include, as appropriate, maximum plasma drug concentration (Cmax), time to maximum plasma drug concentration (Tmax), time of last quantifiable plasma drug concentration (Tlast), area under the plasma concentration versus time curve from time 0 to 24 hours postdose (AUC0-24), plasma drug concentration at 24 hours postdose (C24); apparent volume of distribution (Vz/F), terminal elimination half-life (t½), apparent oral clearance (CL/F), and accumulation ratio (R).
- Pharmacodynamic parameters of pralsetinib: changes in tumor/blood including, but not limited to, changes in blood calcitonin and carcinoembryonic antigen (CEA) (MTC patients); and changes in tumor biomarker levels (DUSP6 and SPRY4) levels (all patients).

1.3.1.3 Exploratory Endpoints

- Levels of exploratory blood and tumor markers (DNA, RNA and protein) as compared to antineoplastic activity, and/or toxicity.

1.3.2 Phase 2 Endpoints

Phase 1 patients treated at MTD/RP2D will be pooled with Phase 2 patients for Phase 2 endpoints accordingly.

1.3.2.1 Primary Endpoints

- ORR by patients' disease type, and/or RET-altered status if applicable, and/or prior treatment status if appropriate.
- Overall safety profile of pralsetinib, as assessed by the type, frequency, severity, timing, and relationship to study drug of any AEs, SAEs, changes in vital signs, ECGs, and safety laboratory tests.

1.3.2.2 Secondary Endpoints

- DOR, CBR, DCR, PFS, and OS in all patients by disease type and/or RET-altered status, if applicable, and/or prior treatment status, if appropriate.

- RET gene status (ie, gene fusion partner or primary mutation and, for MTC, whether hereditary or sporadic) and correlation between RET gene status and ORR, CBR, DOR, DCR, and other measures of antineoplastic activity (in plasma and/or tissue) in all patients according to their disease type and/or RET-altered status, if applicable, and/or prior treatment status, if appropriate.
- PK parameters of pralsetinib: Pharmacokinetic parameters of interest will include, as appropriate, maximum plasma drug concentration (Cmax), time to maximum plasma drug concentration (Tmax), time of last quantifiable plasma drug concentration (Tlast), area under the plasma concentration versus time curve from time 0 to 24 hours postdose (AUC0-24), plasma drug concentration at 24 hours postdose (C24); apparent volume of distribution (Vz/F), terminal elimination half-life (t½), apparent oral clearance (CL/F), and accumulation ratio (R).
- ECG Assessment: In Phase 2, the effects of pralsetinib on ECG parameters will be evaluated for approximately 20 patients using 12-lead ECGs extracted from continuous recordings (12-lead Holter) on C1D1 and C1D15. Individual ECGs will be extracted in replicate from the 12-lead Holter recordings at specified time points and will be evaluated by a central laboratory. QT intervals will be measured from lead II and will be corrected for heart rate (QTc) using Fridericia's correction factors (QTcF). The primary QTc parameter will be QTcF. Secondary parameters (heart rate, PR, and QRS, and T-wave morphology) will also be evaluated. Potential effects of pralsetinib will be evaluated as change from predose baseline heart rate, PR, QRS, and QTcF by postdose time point. For the purpose of QT assessment, exposure-response analysis will be performed on the relationship between pralsetinib systemic levels and change in QTcF.
- Pharmacodynamic parameters of pralsetinib: changes in tumor/blood including, but not limited to, changes in blood calcitonin and CEA and biochemical response rate (MTC patients only).
- Intracranial response rate among patients with NSCLC who have measurable (target by RECIST v1.1) lesions in the brain, and time to intracranial progression among all patients with NSCLC.

1.3.2.3 Exploratory Endpoints

- Changes in patient-reported outcomes as assessed by the European Organization for Research and Treatment of Cancer Core QoL Questionnaire (EORTC QLQ-C30) instruments.
- Changes in disease-related symptoms as reported by bowel movement history for MTC patients.
- ORR, CBR, DCR, PFS for patients previously treated with a selective RET tyrosine kinase inhibitor.
- Intracranial response rate among patients with tumor types other than NSCLC who have measurable (target by RECIST v1.1) lesions in the brain, and time to intracranial progression among all patients with tumor types other than NSCLC.

1.4 SAMPLE SIZE JUSTIFICATION

1.4.1 Phase 1 (Dose-escalation)

The dose escalation part of the study (Phase 1) employs the local BOIN design (Liu and Yuan, 2015) to find the MTD. The BOIN design is implemented in a simple way similar to the traditional 3+3 design but is more flexible and possesses superior operating characteristics that are comparable to those of the more complex model-based designs, such as the continual reassessment method (CRM).

The target toxicity rate for the MTD is 30%. Alternatives under which decision errors are minimized are: 18% (subtherapeutic) and 42% (overly toxic). To avoid assigning too many patients to the overly toxic doses, a dose level will be eliminated (and any planned doses that are higher) when the posterior probability is greater than 95% that the toxicity rate of a dose level is >30%, given the number of patients (≥ 3) and DLTs observed at the dose level. Dose escalation will continue to enroll and treat patients in cohorts of size 3-6 (1-3 for the first 3 dose levels) until 12 patients are treated and evaluable for DLT at one dose level. The total number of patients to be enrolled during the dose escalation part of the study will vary depending on the underlining dose-toxicity curve and the number of dose levels tested prior to reaching MTD and is estimated to be approximately 20 to 50 patients.

1.4.2 Phase 2 (Dose-expansion at the MTD/RP2D)

- Group 1: The sample size of approximately 80 RET-fusion NSCLC patients who previously received treatment with a platinum-based chemotherapy will provide > 95% power at the 2-sided significance level of 0.05 for testing the assumption of the null hypothesis ORR=0.23 versus the alternative ORR=0.5.
- Group 2: The sample size of approximately 170 treatment naïve (1st line) RET-fusion NSCLC patients will provide >90% power at the 2-sided significance level of 0.05 for testing the assumption of the null hypothesis ORR=0.48 versus the alternative ORR=0.61.
- Group 3: The sample size of approximately 65 MTC patients previously treated with cabozantinib and/or vandetanib will provide > 90% power at the 2-sided significance level of 0.05 for testing the assumption of the null hypothesis ORR=0.2 versus the alternative ORR=0.4.
- Group 4: The sample size of approximately 40 MTC patients not previously treated with cabozantinib or vandetanib will be enrolled for exploratory analysis.

- Group 5: The sample size of approximately 100 patients who have solid tumors with a RET fusion previously treated with SOC, have previously received SOC appropriate for their tumor type (unless there is no accepted standard therapy for the tumor type or the Investigator has determined that treatment with standard therapy is not appropriate), and must not eligible for any of the other groups. This sample size will provide >90% power at the 2-sided significance level of 0.05 for testing the assumption of the null hypothesis ORR=0.1 versus the alternative ORR=0.3.
- Group 6: The sample size of approximately 20 patients who have RET-fusion solid tumors that failed prior selective-RET inhibitor will be enrolled for exploratory analysis.
- Group 7: The sample size of approximately 20 patients who have solid tumors with an activating RET mutation previously treated with SOC will be enrolled for exploratory analysis.
- Group 8: The sample size of approximately 30 RET-fusion NSCLC patients that have failed treatment with prior platinum-based chemotherapy will be enrolled by assuming the observed ORR from 27% to 50% based on the preliminary data.
- Group 9: The sample size of approximately 30 MTC patients that were not previously treated with systemic therapy (except prior cytotoxic chemotherapy is allowed) for the advanced or metastatic disease will be enrolled by assuming the observed ORR from 27% to 50% based on the preliminary data.

2. POPULATIONS FOR ANALYSIS

2.1 SAFETY POPULATION

The Safety Population includes all patients who have received at least 1 dose of study drug regardless of starting dose levels. The Safety Population will be the primary population for safety analysis unless otherwise specified. Patients will be analyzed based on the initial dose prescribed on Day 1, regardless of phases.

Patients will be further categorized into different subgroups as described in Section 3.6.4.

Prior selective RET-inhibitor treated patients will be explored separately and will not be included in any defined safety subgroups but will be included in overall Safety Population.

2.2 EFFICACY POPULATION

The Efficacy Population includes all patients in the Safety Population who are dosed on or prior to a certain enrollment date, which will be defined in CSR or submission documents. The Efficacy Population will be the primary population for analysis of efficacy endpoints (except for ORR, best overall response [BOR], CBR, DCR, and DOR) unless otherwise specified. Patients will be analyzed based on the initial dose prescribed on Day 1, regardless of phases.

Similarly, patients will be further categorized into different subgroups in Section 3.6.4.

Prior selective RET-inhibitor treated patients will be explored separately and will not be included in any defined efficacy subgroups but will be included in overall Efficacy Population.

2.3 RET-ALTERED MEASURABLE DISEASE POPULATION

The RET-altered Measurable Disease (RAMD) Population includes Efficacy Population patients who have measurable (target) disease per RECIST v1.1 (or RANO, if appropriate for tumor type) at baseline according to blinded independent central review (BICR) and sufficient evidence of a RET alteration. The RET altered Measurable Disease Population will be the primary population for analysis of ORR, BOR, CBR, DCR, and DOR.

Similarly, patients will be further categorized into different subgroups in Section 3.6.4.

Prior selective RET-inhibitor treated patients will be explored separately and will not be included in any defined efficacy subgroups.

2.4 RESPONSE-EVALUABLE POPULATION

Response-Evaluable (RE) Population includes Efficacy Population patients who have measurable (Target) disease per RECIST v1.1 (or RANO, if appropriate for disease type) at baseline and at least one evaluable post-baseline disease response assessment (based on BICR data) and have experienced no major protocol violation. The RE Population will be used as a sensitivity analysis for ORR, DOR, CBR, and DCR.

The following criteria will lead to exclusion from the RE Population:

- Patient has another known primary driver alteration other than RET identified by central circulating tumor DNA (ctDNA)/tumor tissue assay at baseline.
    - RET-mutation MTC, such as HRAS or KRAS
    - RET-fusion thyroid, such as BRAF, NRAS, or KRAS
    - RET-fusion NSCLC, such as EGFR, ALK, ROS1, or BRAF
    - RET-fusion solid tumor other than NSCLC and thyroid, with any known co-driver alterations identified for the disease type
- Any additional major protocol deviations identified by the medical review of the data that could lead to exclusion from the RE Population will be documented and reported in the CSR or submission documents.

The RE Population will be used for primary efficacy endpoint as a sensitivity analysis for ORR, BOR, CBR, and DCR specified in Section 4.6.1.

2.5 SUB-POPULATION

2.5.1 Central Nervous System Metastases NSCLC Sub-population

Central nervous system (CNS) metastases NSCLC sub-population will include RET-fusion positive NSCLC patients who have had measurable (target) lesion(s) in CNS/brain, including brainstem, cerebellum, frontal lobe, temporary lobe, occipital lobe, parietal lobe, frontoparietal, frontotemporal, temporaloccipital, temporalparietal, and parietolccipita at baseline according to RECIST v1.1 by BICR data and have not had radiotherapy(ies) or radiosurgery(ies) to brain within 2 months before dosed with pralsetinib.

3. GENERAL STATISTICAL CONSIDERATIONS

3.1 RANDOMIZATION, STRATIFICATION, AND BLINDING

This is an open label, single arm study with no randomization or stratification.

3.2 MULTIPLICITY ADJUSTMENT

No multiplicity adjustment is planned in this study.

3.3 DATA ANALYSIS GENERAL INFORMATION AND DEFINITION

Summary statistics for continuous variables will include n (non-missing observations), mean, standard deviation (StdDev), minimum, median, and maximum. Summary statistics for categorical variables will be presented in terms of frequencies and percentages. Time to event data will be summarized and analyzed using Kaplan-Meier (KM) method, which the estimated median with 95% confident intervals (CIs) will be included.

3.3.1 Study Drug

Study drug or study treatment used in the rest of document refers to pralsetinib. Study drug or study treatment and pralsetinib are interchangeable in this document.

3.3.2 Day 1 and Other Days

Date of first dose of pralsetinib (or Cycle 1 Day 1) is defined as the day of the first administration of study drug in the study, i.e., after enrollment. First dose refers to first dose in study unless specified otherwise. There is no Day 0 in any analysis.

Date of last dose of pralsetinib is defined as the date of last administration of study drug (last dose) in the study. For patients who are still with study drug treatment and last dose date is missing, the cutoff date (i.e., database snapshot date) will be used.

3.3.3 Study Day Derivation

Calculations using dates will adhere to the following conventions:

- Study day for a date of interest (target date) is calculated as
- Study Day = target date – first dose date + 1, if target date is on or after Day 1;

- Study Day = target date – first dose date, otherwise.

Note that negative study days are reflective of observations obtained prior to the first dose administration date. First study drug administration dates should always be known. There is no Day 0 in any derivation.

- Age (in years) at informed consent is calculated using the following formula
- Age at informed consent (in years) = (year of consent) - (year of date of birth (DOB)) if passed birthday;
- Age at informed consent (in years) = (year of consent) - (year of DOB) - 1 if otherwise.

This is equivalent to the following:

[(year of consent) - (year of DOB)] – [(month of consent) ≤ (month of DOB)] + [(month of consent) = (month of DOB) and (day of consent) ≥ (day of DOB)]

3.3.4 Duration Derivation

Unless otherwise specified for a specific variable, duration variables will be derived according to the following rules:

- Duration (in days) = (end date – start date +1)
- Duration (in weeks) = (end date – start date +1)/ 7
- Duration (in months) = (end date – start date +1)/ 30.4375
- Duration (in years) = (end date – start date +1)/ 365.25.

Duration variables that are to be expressed in units greater than day will be rounded to 1 decimal place.

3.3.5 Baseline Values

In general, baseline is defined as the last observation prior to first dose of study drug, including pre-dose value or the last available (including unscheduled) value before Day 1 if Day 1 pre-dose value is unavailable unless otherwise specified.

3.3.6 Last Contact Date(s)

Last contact is the date of last assessment(s), medication, procedure, last follow-up, and/or adverse event date, etc., of a patient.

3.4 METHODS FOR HANDLING MISSING DATA

Refer to Section 7.1 for detailed date imputation guidelines.

3.5 VISIT WINDOW(S)

Visits will be windowed. Data are summarized by visit following the visit windows reported in Table 1 when appropriate (e.g. laboratory parameters).

If multiple assessments regardless of scheduled assessment or unscheduled assessment occur within a visit window, the assessment closer to the target day will be used. In case of ties, i.e. with equal distance to the target day, the value from the day before the target day shall be used.

If there are two assessment records occurred on the same day, the scheduled one assessment be used, if available. Otherwise, the earlier assessment will be used.

Table 1 Visit Windows

Visit	Start Day	Target Day	End Day
Day 1 (Cycle 1 Day 1)	1	1	1
Week 1 (Cycle 1 Day 8)	2	8	11
Week 2 (Cycle 1 Day 15)	12	15	18
Week 3 (Cycle 1 Day 22)	19	22	25
Week 4 (Cycle 2 Day 1)	26	29	36
Week 6 (Cycle 2 Day 15)	37	43	50
Week 8 (Cycle 3 Day 1)	51	57	71
Week 12 (Cycle 4 Day 1)	72	85	99
Week 4*(x-1) (Cycle x Day 1)	(x-1)*28-12	(x-1)*28+1	(x-1)*28+15
End of Treatment (EOT)			

EOT, assessment at end of treatment visit. Assessment at end of treatment visit will not be windowed in other visits.

3.6 POOLING STRATEGIES

3.6.1 Grouping Patients by Age

Patients will be pooled based on their age at informed consent.

- Age < 65 years
- Age ≥ 65 years

3.6.2 Pooling Sites by Geographic Region(s)

Sites will be pooled based on their geographic location with the following pooling method.

- Geographic Region
    - USA
    - Europe
    - Asia

3.6.3 Grouping Patients by Race

Patients will be grouped based on their race with the following pooling method.

- Asian, patients' race is Asian
- White, patients' race is White
- Others, patients' race is not Asian or White

3.6.4 Combining Disease Types and RET alteration Status

RET-fusion or RET-mutation positive is based by either central lab assessment test or local lab assessment or both obtained on a sample(s) collected prior to patients' first dose date. The central lab assessment includes analysis of tumor sample tissue through next generating sequencing (NGS) method or blood plasma by ctDNA NGS method.

The disease types and/or RET alteration status will be combined and grouped according to the following rules. For both RET-fusion positive and RET-mutation positive patients, patients' RET alteration status will be based on their disease type. The primary RET alteration status is RET-fusion for NSCLC patients, RET-mutation for MTC patients, RET fusion for all other solid tumors that bear a RET fusion. The primary RET alteration status is used to group patients into different subgroups.

- RET-fusion, including RET-fusion positive patients.
- RET-fusion NSCLC, including RET-fusion positive NSCLC patients, tested positive either by central lab assessment, or local lab assessment test or both
- RET-fusion NSCLC prior systemic treated patients, including RET-fusion positive NSCLC patients previously treated with systemic therapy(ies)
- RET-fusion NSCLC prior platinum treated patients, including RET-fusion positive NSCLC patients previously treated with platinum-based chemotherapy(ies) regardless of neoadjuvant/adjuvant setting.
- RET-fusion NSCLC no prior platinum treated patients, including RET-fusion positive NSCLC patients not previously treated with platinum-based chemotherapy(ies)
- RET-fusion NSCLC non-platinum systemic treated patients, including RET-fusion positive NSCLC patients not previously treated with platinum-based chemotherapy(ies) but treated with other systemic therapy(ies)
- RET-fusion NSCLC no prior systemic treated patients, including RET-fusion positive NSCLC patients without any previous systemic treatment.
- RET-fusion thyroid, including RET-fusion positive thyroid patients
- RET-fusion thyroid prior systemic treated patients, including RET-fusion positive thyroid patients previously treated with systemic therapy(ies)
- RET-fusion others, including RET-fusion positive patients other than RET-fusion NSCLC and RET-fusion thyroid patients
- MTC, all MTC patients regardless of RET alteration status
- RET-mutation MTC, all RET-mutation positive MTC patients tested positive by central/local lab assessment
- RET-mutation MTC prior systemic treated patients, including RET-mutation positive MTC patients previously treated with systemic therapy(ies)
- RET-mutation MTC prior cabozantinib and/or vandetanib treated patients, including RET-mutation positive MTC patients previously treated with cabozantinib and/or vandetanib therapy(ies)
- RET-mutation MTC prior cabozantinib and vandetanib treated patients, including RET-mutation positive MTC patients previously treated with both cabozantinib and vandetanib

- RET-mutation MTC prior no cabozantinib and/or vandetanib treated patients, including RET-mutation positive MTC patients not previously treated with either cabozantinib or vandetanib
- RET-mutation MTC no prior systemic therapy treated patients, including RET-mutation positive MTC patients not previously treated with systemic therapy(ies)
- No/unknown RET-mutation MTC patients, including MTC patients with no or unknown RET-mutation status regardless of prior treatment(s) before starting pralsetinib treatment
- No RET-mutation MTC patients, including RET-mutation negative MTC patients
- Unknown RET-mutation MTC patients, including RET-mutation status unknown MTC patients
- RET-altered Thyroid, including RET-mutation positive MTC patients and RET-fusion positive thyroid patients.
- RET-mutation others, including all RET-mutation positive disease types other than MTC
- No/Unknown RET alteration Other solid tumor, including patients with no RET alteration or unknown RET alteration status other than MTC
- Prior selective RET-inhibitor treated patients, including all patients previously treated with selective RET-inhibitor, such as LOXO-292, regardless of disease type(s) and RET alteration status. Prior selective RET-inhibitor treated patients are not included in any subgroups defined above

3.6.5 Dose Levels

3.6.5.1 Grouped Dose Levels I

The starting dose will be grouped for efficacy analysis endpoints, ORR, BOR, CBR, DCR, DOR, PFS, OS, etc., Safety, Efficacy Population, RAMD Population, and RE Population subgroups, defined in Section 3.6.4, according to the following rules,

- 400 mg QD
- All, including all QD dose levels (30 mg QD – 600 mg QD) and BID dose levels (100 mg/100 mg BID and 200 mg/100 mg BID)

3.6.5.2 Grouped Dose Level II

For other analysis endpoints based on overall patients, i.e. all Safety Population, the starting dose will be grouped for analyses according to the following rules,

- ≤300 mg QD, patients initially treated with 30 mg QD, 60 mg QD, 100 mg QD, 200 mg QD, and 300 mg QD
- 400 mg QD, patients initially treated at 400 mg QD
- BID, patients initially treated with 100 mg/100 mg BID and 200 mg/100 mg BID of pralsetinib

- All, including all QD dose levels (30 mg QD – 600 mg QD) and BID dose levels (100 mg/100 mg BID and 200 mg/100 mg BID).

3.6.6 Grouping Patients by baseline Weight

Patients will be pooled based on their baseline weight as follows:

- Weight < 60 kg
- Weight ≥ 60 kg and ≤ 75 kg
- Weight > 75 kg

4. STATISTICAL ANALYSIS

The endpoints will be analyzed by combined disease types and RET alteration status and grouped dose levels accordingly.

The grouped dose level I will be used on efficacy and safety endpoints for prespecified subgroups, defined in Section 3.6.4, based on RAMD Population, Efficacy Population, Safety Population, and RE Population, respectively. The grouped dose level II will be applied for all Safety Population. However, the primary efficacy and safety analyses will be conducted mainly for patients started at 400 mg QD of pralsetinib, unless otherwise specified. The efficacy and safety analyses for all patients, regardless of dose level, will be provided as supportive analyses.

The efficacy endpoints will be analyzed for prespecified subgroups, defined in Section 3.6.4, based on RAMD Population and Efficacy Population, respectively. The ORR, BOR, CBR, DCR, and DOR will be analyzed primarily based on RAMD Population and supportively based on Efficacy Population. Other efficacy endpoints will be analyzed primarily based on Efficacy Population. In addition, the efficacy endpoints ORR, BOR, CBR, DCR, DOR, intracranial ORR (including intracranial BOR, CBR, DCR, and DOR) will be analyzed based on RE Population.

The safety endpoints will be analyzed for those prespecified subgroups and “All” patients based on Safety Population. Other endpoints, including disposition, demographics, baseline characteristics, medical history, prior/concomitant medication, protocol deviations, treatment exposure and modification, etc., will be analyzed for prespecified subgroups, and “All” patients based on Efficacy, RAMD and Safety Population, respectively, unless otherwise specified in each section.

The prior selective RET-inhibitor treated patients will not be included in any subgroups but will be included in “All” patients.

4.1 STUDY PATIENTS

4.1.1 Analysis Population

A summary of analysis population by starting dose and "All" will be presented for the following items.

- Safety Population
  - RET-fusion
    - RET-fusion NSCLC
      - RET-fusion NSCLC prior systemic treatment
      - RET-fusion NSCLC prior platinum treatment
      - RET-fusion NSCLC no prior platinum treatment
        - RET-fusion NSCLC prior non-platinum systemic treatment
        - RET-fusion NSCLC no prior systemic treatment
      - RET-fusion thyroid
        - RET-fusion thyroid prior systemic therapy treated patients
        - RET-fusion others
    - MTC
      - RET-mutation MTC
        - RET-mutation MTC prior systemic therapy treated patients
        - RET-mutation MTC prior cabozantinib and/or vandetanib treated patients
          - RET-mutation MTC prior cabozantinib and vandetanib treated patients
        - RET-mutation MTC prior no cabozantinib and/or vandetanib treated patients
          - RET-mutation MTC no prior systemic therapy treated patients
      - No/unknown RET-mutation MTC patients
        - No RET-mutation MTC patients
        - Unknown RET-mutation MTC patients
    - RET-altered thyroid cancer patients
    - RET-mutation others
    - No/Unknown RET alteration status solid tumors other than MTC
    - Prior selective RET-inhibitor treated
    - All patients at all doses
- Efficacy Population

The layout for Efficacy Population will follow the same format for Safety Population.

- RET-altered Measurable Disease Population
- The layout for Efficacy Population will follow the same format for Safety Population.
- Response Evaluable Population

The layout for RE Population will follow the same format for Safety Population.

4.1.2 Patient Disposition

The number and percentage of patients will be summarized.

- Safety Population
- Efficacy Population
- RET-altered Measurable Disease Population
- Response Evaluable Population
- Discontinued from Treatment
- Continuing Treatment
- Discontinued from Study
- Continuing Study Follow-up
- Reasons for treatment discontinuation will be summarized with the following categories collected on the case report form (CRF).
    - Disease Progression
    - Adverse Event
        - Treatment Related Adverse Event
        - Adverse Event Except Disease Progression
    - Death
    - Lost to Follow-up
    - Protocol Deviation
    - Withdrew Consent
    - Pregnancy
    - Investigator's Decision
    - Administrative/Other
    - Sponsor Decision
- Reasons for study discontinuation will be summarized with the following categories collected on the CRF.
    - Disease Progression
    - Adverse Event
    - Treatment Related Adverse Event

- Death
- Lost to Follow-up
- Protocol Deviation
- Withdrew Consent
- Pregnancy
- Investigator's Decision
- Administrative/Other
- Initial of Another Antineoplastic Therapy
- Sponsor Decision

A by-patient listing including each treated patient will be provided.

4.1.3 Protocol Deviations

Deviations from the protocol, as defined in the protocol and protocol deviation plan, will be documented, reviewed, and categorized as important or non-important. Important protocol deviations will be summarized descriptively.

Prior to each database snapshot and final database lock, important deviations will be further categorized as major or minor based on medical review with major protocol deviations potentially leading to exclusion from the RE Population. Major protocol deviations will also be summarized descriptively.

A by-patient listing of patients with protocol deviations in the safety population was provided.

4.2 DEMOGRAPHICS AND BASELINE DISEASE CHARACTERISTICS

Demographic and baseline disease characteristic data will be summarized.

4.2.1 Demographics

The number and percentage of patients in each of the following categories will be presented.

- Age group
  - < 65 years
  - ≥ 65 years
    - ≥ 65 to 74 years
    - ≥ 75 to 84 years
    - ≥ 85 years
- Sex

- Ethnicity
- Race
- Race group (Asian, White, Others)
- Geographic Region
    - USA
    - Europe
    - Asia
- Weight
    - < 60 kg
    - ≥ 60 kg and ≤ 75 kg
    - > 75 kg
    -

Age (Years), height (cm), weight (kg), body mass index (BMI) (kg/m2), and body surface area (BSA) will be summarized descriptively.

BMI will be calculated as: BMI (kg/m2) = (weight in kg)/ (height in meter)2.

BSA will be calculated based on Dubois and Dubois formula (Dubois D, Dubois EF, 1916) as

$$BSA\ (m^2) = 0.007184 \times (\text{height in cm})^{0.725} \times (\text{weight in kg})^{0.425}.$$

Individual demographics data will be listed in a by-patient listing.

4.2.2 Baseline Disease Characteristics

The number and percentage of patients in each of the following categories will be presented.

- The Eastern Cooperative Oncology Group (ECOG) performance status (0, 1, 2 if any, 3 if any, 4 if any)
- Primary tumor site (Lung, Thyroid, or Other)
- Metastatic disease status
    - Yes
    - No
- Target/Non-Target Lesion Location, Target/non-target lesion location will be based on BICR data
- History of CNS metastases,

    including patients who had medical history metastases site in CNS/Brain from CRF data, and patients whose target or non-target lesion(s) location were in CNS/Brain, brainstem, cerebellum, frontal lobe, temporal lobe, parietal lobe,

occipital lobe, frontoparietal, frontotemporal, temporaloccipital, temporalparietal, parietolccipital at baseline according to RECIST v1.1 by BICR data

- TNM Stage at initial diagnosis
- Current stage at screening visit
- Histology type
    - Lung cancer patients
        - Adenocarcinoma
        - Squamous
        - Undifferentiated
        - Other
    - Thyroid cancer patients
        - Medullary
        - Papillary
        - Follicular
        - Anaplastic
        - Other
    - Other
        - Cancer type specified from database.
- Smoking history for NSCLC patients (Never smoked, Former smoker, Current smoker, or Unknown)
- Prior line of therapy

  The prior line of therapy is defined as the number of eligible systemic therapy(ies) before enrollment. The systemic therapies are provided by medical review. The derivation of the prior line of therapy is documented in Section 7.2.

  The prior line of therapy will be summarized. In addition, the prior line of therapy will also be categorized into 0, 1, 2, 3, 4, 5, and ≥6 accordingly.
- RET gene status (hereditary, or sporadic, or others) for MTC patients.
- The derivation of RET gene status for MTC patients is documented in Section 7.3.
- Primary RET alteration mutation status; Patient's status will be classified according to the primary driver RET genotype according to the hierarchy order below
- RET fusion
    - KIF5B
    - CCDC6
    - NCOA4
    - Other
    - Unknown

- RET mutation
    - M918T
    - Cysteine rich domain, including patients with single nucleotide variants of or short indels that include the following residues: C609, C611, C618, C620, C630 and/or C634 of RET
    - V804X, including patients with RET-mutation status V804M and V804L
    - Other
    - Unknown

Individual baseline characteristics, including prior PD-1/PD-L1 status, will be listed in by-patient listings. Patients with both RET-fusion positive and RET-mutation positive will be grouped by primary RET alteration status in disease characteristics tables, detailed in Section 3.6.4.

A consolidated listing for RET-fusion and RET-mutation information collected either from local testing method, or tumor tissue by NGS or plasma by central circulating tumor DNA (ctDNA) testing results obtained on or prior to first dose date will also be provided.

A listing and summary tabulation providing additional details from local pathology reports for the RET mutation molecular testing results for predefined subgroups that include the following information: the test method, mutation identified, fusion partner identified, in-frame fusion (Y/N), presence of concomitant oncogenic driver mutation other than RET (Y/N), oncogenic driver identified (if yes) and if tissue is available for re-testing will be provided.

4.3 MEDICAL HISTORY

The medical history is coded with the most current version of the Medical Dictionary for Regulatory Activities (MedDRA). All medical history will be summarized by system organ class (SOC) and preferred term (PT).

All medical history data will be presented in a by-patient listing.

4.4 PRIOR AND CONCOMITANT MEDICATIONS

4.4.1 Prior and Concomitant Medications

Prior and concomitant medication will be coded with the most current version of the World Health Organization Drug (WHODrug) Dictionary. Any therapies that are discontinued before the first dose of study treatment (Day 1) will be considered as prior medication. Concomitant medications are all medications taken from Day 1 to 30 days after the last dose of study drug. Therapies taken before Day 1 with missing end date will be considered as concomitant medications. If the last dose date of study drug is not available, the cutoff date is used in place of the last dose date.

The following analyses will be provided.

- The number and percentage of patients taking prior medications and/or significant non-drug therapies will be summarized by anatomical class (ATC, ATC code level 3) and PT,
- The number and percentage of patients taking concomitant medications and/or significant non-drug therapies will be summarized and listed by ATC and PT

A patient taking a same medication multiple times is counted only once for the specific PT within an ATC.

Prior and concomitant medications will be listed in a by-patient listing.

4.4.2 Prior Antineoplastic Therapy

Prior antineoplastic therapies are recorded and coded using the most current version of the WHO Drug Dictionary. These therapies will be further grouped into systemic therapy(ies), MKI, chemotherapy(ies), platinum-based chemotherapy(ies), immunotherapy(ies), selective RET-inhibitor, and others by medical review.

The number and percentage of patients previously treated with each category will be summarized.

- Prior antineoplastic systemic therapy (Yes, or No)
    - Multikinase inhibitor(s)
        - Only cabozantinib, patients treated with cabozantinib other than vandetanib
        - Only vandetanib, patients treated with vandetanib other than cabozantinib
        - Both cabozantinib and vandetanib, patients treated with cabozantinib and vandetanib
        - Cabozantinib or vandetanib, patients treated with cabozantinib and/or vandetanib
        - prior lenvatinib and/or sorafenib
        - Other MKI therapy(ies), patients treated with MKI therapy(ies) other than cabozantinib, vandetanib, lenvatinib, and sorafenib regardless of the above 4 types of MKI therapies.
    - Chemotherapy
        - Platinum-based chemotherapy
        - Other chemotherapy, patients treated with chemotherapy(ies) other than platinum-based chemotherapy regardless of prior platinum-based chemotherapy treatment
    - Immunotherapies
        - Programmed cell death protein 1/ programmed death ligand 1 (PD-1/PD-L1) inhibitors

        - Other immunotherapies, patients treated with immunotherapy(ies) other than PD-1/PD-L inhibitors regardless of prior PD-1/PD-L1 inhibitors
    - Selective RET-inhibitor
    - Others
- Prior radiation therapy (Yes, or No)
- Prior cancer related surgeries or procedures (Yes, or No)
- The following item will be added for RET-mutation MTC, RET-fusion thyroid within prior systemic therapy.
- prior radioactive iodine (RAI)

A by-patient listing of prior radiotherapy and prior cancer related surgery or procedures will also be provided.

4.5 STUDY TREATMENTS AND EXTENT OF EXPOSURE

A summary of study drug exposure, including cumulative dose, dose intensity, relative dose intensity (RDI), duration of treatment, and the proportion of patients with dose modifications will be produced.

4.5.1 Treatment Duration and Exposure

Duration of treatment (days) = (treatment end date– treatment start date + 1).

Duration of treatment (weeks) = (treatment end date– treatment start date + 1) / 7.

Duration of treatment (months) = (treatment end date – treatment start date + 1)/30.4375.

The treatment start date is the first dose date of study drug, and the treatment end date is the last dose date of study drug or data cutoff date if patients are still ongoing with the treatment, whichever is earlier.

Descriptive statistics will be provided for treatment duration in weeks and months.

Treatment duration will also be classified into the following categories.

- < 6 months
- ≥ 6 months to < 12 months
- ≥ 1 year to 2 years
- ≥ 2 years to 3 years
- ≥ 3 years

4.5.2 Cumulative Dose

Cumulative dose (mg) is defined as sum of all dose taken. The dosage will be counted as 0 for days when the study drug is not taken.

4.5.3 Average Daily Dose

Average daily dose (mg) is defined as the cumulative dose divided by the number of days dosed. Each patient has an average daily dose.

4.5.4 Dose Intensity

Dose intensity (mg/day) is defined as the cumulative dose divided by the treatment duration (in days).

4.5.5 Relative Dose Intensity

RDI (%) is defined as dose intensity / planned dose intensity x100. Planned dose intensity is based on initial assigned daily dose.

RDI will be summarized descriptively as a continuous variable. The RDI will also be categorized into <75%, 75% to <90%, 90% to 120%, 120 to 150%, and ≥150% and be presented accordingly.

Cumulative dose, average daily dose, dose intensity, RDI will also be summarized for every cycle, i.e., 4 weeks.

A by-patient listing of study drug including treatment duration, cumulative dose, average daily dose, dose intensity, planned initial dose, and RDI will be provided.

4.5.6 Dose Modification

The number and percentage of patients who had dose modification and reasons for dose modification will be summarized as follows. The dose modification will also be further categorized as 0 (no dose modification), 1 (one dose modification), 2 (two dose modifications), and ≥ 3 (at least three dose modifications).

- Dose escalated
- Dose interrupted
    - Dose interrupted due to adverse event (AE)
    - Dose interrupted due to treatment related AE
- Dose discontinued
    - Dose discontinued due to AE
    - Dose discontinued due to treatment related AE
- Dose reduced
    - Dose reduced due to AE

- Dose reduction due to treatment related AE

- Dose missed
  - Dose missed due to AE
  - Dose reduced, or dose interrupted, or dose missed due to AE

Details of dose modifications will also be provided in a by-patient listing.

4.6 EFFICACY ANALYSIS

Endpoints involving response assessment will be primarily based on BICR data. The investigator assessment will also be analyzed using the same analysis method as a supportive analysis. The tumor response and progression will be assessed by RECIST v1.1 criteria (Eisenhauer version 1.1, 2009) (or RANO criteria [Wen Madcdonald et al, 2000], if appropriate).

The efficacy analyses for ORR, BOR, CBR, DCR, DOR will be primarily summarized for prespecified subgroups, defined in Section 3.6.4, based on RAMD Population and also analyzed based on Efficacy Population as supportive analyses, respectively. The efficacy analyses for PFS, OS will be summarized for predefined subgroups based on Efficacy Population in Section 3.6.4, respectively, unless otherwise specified in the corresponding section. The sensitivity analysis of the primary efficacy analyses for ORR, BOR, CBR, DCR, DOR will also be conducted based on RE Population and Efficacy Population. The intracranial ORR, including BOR, CBR, DCR, DOR, will be analyzed based on RAMD, Efficacy, and RE Population.

The efficacy endpoints per analysis population are summarized in Table 2.

Table 2 Efficacy Endpoints and Analysis Population

	RET-altered Measurable Population	Efficacy Population	Response Evaluable Population
ORR, BOR, CBR, DCR, DOR	X	X	X
Intracranial ORR, BOR, CBR, DCR, DOR*	X	X	X
PFS, and intracranial PFS*		X	
OS		X	
EORTC QoL		X	
Bowel function movement		X	

* RET-fusion NSCLC CNS metatstases sub-population and other solid tumor if applicable.

The efficacy endpoints ORR, BOR, CBR, DCR and DOR assessed by RECIST v1.1 criteria will also be analyzed for RAMD Population treated at 400 mg QD (in either Phase 1 or 2) by subgroups defined in Section 3.6.4, and “All” patients. Patients whose

tumor response and progression assessed by RANO criteria will be analyzed and summarized separately.

Waterfall plots for maximum tumor shrinkage from baseline will be provided for prespecified subgroups defined in Section 3.6.4 based on RAMD and Efficacy Population if baseline and post baseline target lesion measurements are both available assessed by RECIST v1.1. criteria and RANO criteria, respectively and separately.

Forest plots of ORR and 95% CI will be provided for RAMD and Efficacy Population correspondingly.

4.6.1 Primary Efficacy Endpoint

The primary efficacy endpoint of ORR is defined as the proportion of patients with a confirmed response (complete response [CR] or partial response [PR] for at least two assessments with at least 28 days apart and no disease progression [PD] in between) before PD and/or other anticancer therapy. ORR and its two-sided 95% CI, which is based on the exact binomial distribution (Clopper-Pearson), will be presented.

Each patient's best overall response (BOR) will be derived based on RECIST v1.1 (or RANO criteria if appropriate). Patients without post-baseline disease assessments will be imputed with not evaluable (NE) as their BOR. The BOR will be summarized by count and frequency for each category, CR, PR, stable disease (SD), PD, or NE. Patients whose tumor response and progression assessed by RECIST v1.1 or RANO criteria will be summarized and listed accordingly and separately.

Waterfall plots will be provided depicting graphically the maximum percentage shrinkage from baseline in sum of diameters of target lesions assessed by RECIST v1.1 on or prior to first documented disease progression or new subsequent anticancer therapy. Waterfall plots will also be provided separately depicting graphically the maximum percentage shrinkage from baseline in sum of the product of diameters assessed by RANO on or prior to the first documented disease progression or new subsequent anticancer therapy if appropriate.

Forest plots of ORR and 95% CI will be provided for RET altered Measurable Disease Population and Efficacy Population correspondingly.

Individual tumor assessment and BOR will be provided in a by-patient efficacy data listing.

4.6.1.1 RET-fusion NSCLC

ORR will be presented for 1) overall, 2) prior systemic treatment, 3) prior platinum treatment, 4) prior non-platinum systemic treatment, and 5) no prior systemic treatment patients according to grouped dose level I (400 mg QD and All dose levels), respectively

and separately. However, the ORR is mainly conducted for patients started at 400 mg QD of the study drug.

ORR will also be analyzed for 1) – 5) by prior MKI status (yes vs. no), prior chemotherapies other than platinum-based therapies status if applicable, and by prior PD-1/PD-L1 status (yes vs. no), respectively. In addition, ORR will be analyzed by RET genotype, KIF5B, CCDC6, and others; and further analyzed by age group, grouped race, geographic region, and sex, respectively.

The analysis for ORR and DOR will also be summarized for RET-fusion NSCLC patients.

The following ORR analyses will be provided (Table 3).

Table 3 Summary of ORR, BOR, CBR, DCR analysis table(s) for RET-fusion NSCLC patients

	Dose group	
RET-fusion NSCLC *	400 mg QD	All
Overall	X	X
Prior Systemic Treatment	X	X
Prior Platinum Treatment	X	X
Prior non-Platinum Systemic Treatment	X	X
No Prior Systemic Treatment	X	X
Prior MKI Treatment Status		
RET-fusion NSCLC Prior MKI Treatment	X	X
RET-fusion NSCLC No Prior MKI Treatment	X	X
Prior Chemotherapy other than Platinum	X	X
Prior PD-1/PD-L1 Treatment Status		
RET-fusion NSCLC Prior PD-1/PD-L1 Treatment	X	X
RET-fusion NSCLC No Prior PD-1/PD-L1 Treatment	X	X
RET genotype		
KIF5B	X	X
CCDC6	X	X
NCOA4	X	X
Others	X	X
Unknown	X	X
Age group (<65, ≥65)	X	X
Sex (Male, Female)	X	X
Geographic region (USA, Europe, Asia)	X	X
Race (Asian, White, Others)	X	X

	Dose group	
RET-fusion NSCLC CNS Metastases Sub-population	X	X

* 1) – 5) is listed for RET-fusion NSCLC for illustration purpose. The same layout will be used for all items listed in the table.

In addition, the ORR will also be analyzed by prior systemic line of therapy for RET-fusion NSCLC mainly based on RET-altered Measurable Disease Population and supportively based on Efficacy Population, respectively, summarized in Table 4. The ORR may be explored by prior line of therapy and prior platinum treatment, and/or prior PD-1/PD-L1 status.

Table 4 Summary of ORR, BOR, CBR, DCR analysis table(s) for RET-fusion NSCLC patients by prior line of therapy

	Dose group	
RET-fusion NSCLC	400 mg QD	All
Prior line of systemic therapy	X	X
0 Prior line of systemic therapy	X	X
1 Prior line of systemic therapy	X	X
2 Prior line of systemic therapies	X	X
≥3 Prior line of systemic therapies	X	X

The forest plot of ORRs by categories documented in Table 3 and Table 4 and their 95% CI will be provided.

Individual tumor assessment and BOR will be also provided in a by-patient efficacy data listing.

4.6.1.2 RET-mutation MTC

ORR will be presented for 1) overall, 2) prior systemic treatment, 3) prior cabozantinib and/or vandetanib treatment, 4) prior cabozantinib and vandetanib, 5) no prior cabozantinib and/or vandetanib treatment, and 6) no prior systemic treatment patients according to grouped dose level I (400 mg QD and All dose levels), respectively, for RET-mutation MTC subgroup. The ORR will also be analyzed by RET genotype and by age group, sex, geographic region, and race group, RET gene status respectively. The following ORR analyses will be provided (Table 5).

Table 5 Summary of ORR, BOR, CBR, and DCR analyses for RET-mutation MTC Patients

	Dose group	
RET-mutation MTC 1) – 6) **	400 mg QD	All
Overall	X	X
Prior systemic		

	Dose group	
Prior cabozantinib and/or vandetanib	X	X
Prior cabozantinib and vandetanib treated patients	X	X
No prior cabozantinib and/or vandetanib treated patients	X	X
No prior systemic treatment	X	X
RET-genotype		
M918T	X	X
Cysteine rich domain *	X	X
V804X+	X	X
Others	X	X
Age group (<65, ≥65)	X	X
Sex (Male, Female)	X	X
Geographic region (USA, Europe, Asia)	X	X
Race group (Asian, White, Others)	X	X
RET gene status (hereditary, sporadic, other)	X	X

** 1) – 6) is listed for RET-mutation MTC for illustration purpose.

* Patients with C609, C611, C618, C620, C630 and/or C634 of RET-mutation genotype.

+ Patients with V804M and V804L RET-mutation genotype.

In addition, the ORR will also be analyzed by prior line of therapy for RET-mutation MTC subgroup primarily based on RET-altered Measurable Disease Population and supportively based on Efficacy Population, respectively, summarized in Table 6.

Table 6 Summary of ORR, BOR, CBR, DCR analysis table(s) for RET-mutation MTC patients by prior line of therapy

	Dose group	
RET-mutation MTC	400 mg QD	All
Prior line of systemic therapy	X	X
0 Prior line of systemic therapy	X	X
1 Prior line of systemic therapy	X	X
≥2 Prior line of systemic therapies	X	X

The forest plot of ORRs by categories documented in Table 5 and Table 6 and their 95% CI will be provided.

The ORR may be explored by prior line of therapy and prior cabozantinib and/or vandetanib, and/or prior RAI therapy status.

4.6.1.3 RET-fusion Thyroid Cancer

ORR will be presented by 1) overall and 2) prior systemic treatment treated RET-fusion thyroid patients. ORR will also be summarized by RET genotype. In addition, the ORR will be analyzed by age group, sex, geographic region, and race group if applicable. The analyses are summarized in Table 7.

Table 7 Summary of ORR, BOR, CBR, and DCR analyses for RET-fusion thyroid patients

	Dose group	
RET-fusion thyroid 1) – 2) *	400 mg QD	All
Overall	X	X
Prior systemic treatment	X	X
RET genotype		
CCDC6	X	X
NCOA4	X	X
Others	X	X
Age group (<65, ≥65)	X	X
Sex (Male, Female)	X	X
Geographic region (USA, Europe, Asia)	X	X
Race group (Asian, White, Others)	X	X

* 1) – 2) is listed for RET-fusion thyroid for illustration purpose.

In addition, the ORR by prior line of therapy may be also explored for RET-fusion thyroid subgroup if applicable primarily based on RET-altered Measurable Disease Population and supportively based on Efficacy Population, respectively.

4.6.1.4 RET-mutation other than MTC

ORR, BOR, CBR, DCR, and DOR will be presented by grouped dose levels (400 mg QD and All) with other RET-alteration status and disease types for RET-mutation other than MTC patients.

4.6.1.5 RET-fusion solid tumors other than NSCLC and thyroid patients

ORR, BOR, CBR, DCR, and DOR will be presented with other RET alteration status and disease types for RET-fusion Others defined in Section 3.6.4.

4.6.1.6 Other patients

The primary efficacy endpoint across RET-altered Measurable Disease Population prespecified subgroups, and “All” patients will also be provided. In addition, the primary efficacy endpoints with investigator assessment data as a supportive analysis. The prior selective RET-inhibitor treated patients will only be included in “All” patients.

4.6.2 Secondary Efficacy Endpoints

4.6.2.1 Progression Free Survival

PFS is defined as the time from the first dose of pralsetinib to the date of first documented disease progression or death due to any cause, whichever occurs first. Patients without disease progression or death at time of data cutoff will be censored at their last valid assessment. Complete censoring rules are specified in Table 8.

PFS will be analyzed using Kaplan-Meier (KM) methods, the estimated median with two-sided 95% CI and 25th and 75th percentiles will be provided. The confidence interval calculation is based on identity (i.e. linear) transformation. PFS at specific time-points (e.g. 3-, 6-, 9-, 12-, 18-, 24-, 30-month etc. every 6-month after 12-month) will be computed, along with the standard errors using Greenwood's formula (Klen, 2003). PFS will also be displayed with KM plots.

Table 8 Duration of Response and Progression Free Survival Censoring Rules

Situation	Date of Progression or Censoring	FDA Censoring Rules	EMA Censoring Rules
No baseline assessments and alive after 2 scheduled assessments (at least 128 days)	Date of first dose of treatment	Censored	Censored
Progression documented between scheduled visits	Date of radiological assessment showing progression	Event	Event
No progression	Date of last radiological assessment with evidence of no progression (or first dose date if no assessment)	Censored	Censored
New antineoplastic/ non-protocol treatment started prior to progression	Date of last radiological assessment with evidence of no progression on or prior to the start of new antineoplastic treatment	Censored	Event at date of disease progression/death
No progression and new antineoplastic/ non protocol treatment started	Date of last radiological assessment on or prior to the start of new antineoplastic treatment.	Censored	Censored

Situation	Date of Progression or Censoring	FDA Censoring Rules	EMA Censoring Rules
Death before the second scheduled post-baseline assessment if the first scheduled post-baseline assessment is not PD (defined as 128 days after first dose)	Date of death	Event	Event
Death between scheduled assessments	Date of death	Event	Event
Death or progression after missing two or more consecutively scheduled disease assessments (2 more missed scheduled assessments defined by at least x[1] days)	Date of last radiological assessment with evidence of no progression prior to death/progression	Censored	Event at date of disease progression/death

[1] x= 128 days before EOT visit; x=197 days if the death or progression date is after EOT.

EMA, European Medicine Agency; FDA, Food and Drug Administration (US).

The following PFS analyses (Table 9) will be conducted based on BICR data and investigator assessment, and different censoring rules specified (Table 8).

Table 9 Summary of PFS analyses

	Dose group	
	400 mg QD	All
RET-fusion NSCLC 1) – 5)*	X	X
RET-fusion NSCLC CNS Metastases Sub-population	X	X
RET-fusion thyroid 1) -2) *	X	X
RET-fusion solid tumor other than NSCLC and thyroid	X	
RET-mutation MTC 1) – 6) +	X	X

* 1) – 5) and 1) -2) are defined in Section 3.6.4 and Table 3.

+ 1) – 6) are defined in Section 3.6.4 and Table 5.

4.6.2.2 Duration of Response

Duration of response (DOR) will be analyzed for patients with confirmed CR or PR. DOR is defined as the time from first documented response (CR/PR) to the date of first documented disease progression or death due to any cause, whichever occurs first. Patients without confirmed CR or PR will be excluded from this analysis. Patients who are still in response at time of data cutoff will be censored at their last valid assessment. The DOR analysis will be conducted based on BICR data and different censoring rules specified in (Table 8).

Duration of response will be analyzed using KM methods and will include the estimated median with two-sided 95% CI and 25th and 75th percentiles. DOR at specific time-points (e.g. 3-, 6-, 9-, 12-, 18-, 24-, 30-month etc.) will be computed, along with the standard errors using Greenwood's formula (Klen, 2003). Additionally, the proportion of patients with DOR of at least 3, 6, 9, 12, 18, 24, and 30 months will be summarized regardless of censoring status.

The following DOR analyses (Table 10) will be conducted based on BICR data. The DOR analysis will also be produced based on investigator assessment as a supportive analysis for RET-mutation MTC, RET-thyroid, and DOR across RET alteration status and disease types.

Table 10 Summary of DOR analyses

	Dose group	
	400 mg QD	**All**
RET-fusion NSCLC 1) – 5)*	X	X
Age group (<65, ≥65)	X	X
Sex (Male, Female)	X	X
Geographic region (USA, Europe, Asia)	X	X
Race (Asian, White, Others)	X	X
RET-fusion genotype		
KIF5B	X	X
CCDC6	X	X
Others	X	X
RET-fusion NSCLC 1) – 5)*	X	X
Age group (<65, ≥65)	X	X
Sex (Male, Female)	X	X
Geographic region (USA, Europe, Asia)	X	X
Race (Asian, White, Others)	X	X
RET-fusion NSCLC CNS Metastases Sub-population	X	X
RET-fusion solid tumor other than NSCLC and thyroid	X	X
RET-fusion NSCLC by prior line of systemic therapy (0, 1, 2, ≥3)	X	X
RET-fusion thyroid 1) – 2) *	X	X
RET genotype		
CCDC6	X	X
NCOA4	X	X
Others	X	X
RET-fusion thyroid if applicable		

	Dose group	
Age group (<65, ≥65)	X	X
Sex (Male, Female)	X	X
Geographic region (USA, Europe, Asia)	X	X
Race group (Asian, White, Others)	X	X
RET-mutation MTC 1) – 6) [+]	X	X
RET-genotype		
M918T	X	X
Cysteine rich domain [**]	X	X
V804X[++]	X	X
Others	X	X
RET gene status	X	X
RET-mutation MTC by prior line of systemic therapy (0, 1, ≥2)	X	X

[*] 1) – 2) are defined in Section 3.6.4 and Table 3.

[+] 1) – 6) are defined in Section 3.6.4 and Table 5.

[**] Patients with C609, C611, C618, C620, C630 and/or C634 of RET-mutation genotype.

[++] Patients with V804M and V804L RET-mutation genotype.

DOR will be analyzed for the above patient groups if there are confirmed responses in the specified groups. Duration of response will also be displayed with KM plots.

DOR across prespecified subgroups and "All" patients will also be provided with investigator assessment data as a supportive analysis, separately.

4.6.2.3 Clinical Benefit Rate

CBR is defined as the rate of CR or PR, or stable disease which stable disease has been lasting at least 16 weeks (i.e. 4 cycles if 28 days are in one cycle) from the first dose date. CBR will be analyzed and summarized using the same methods as ORR defined in Section 4.6.1.

4.6.2.4 Disease Control Rate

DCR is defined as the proportion of patients with a confirmed CR/PR, or SD, per RECIST v1.1 (or RANO if appropriate). DCR will be analyzed and summarized using the same methods as ORR defined in Section 4.6.1.

4.6.2.5 Overall Survival

OS is defined as the time from the first dose of pralsetinib to the date of death due to any causes. Patients who are still alive or lost to follow-up will be censored at the last known alive date. Last date known alive is defined as the last non-imputed date of any patient record prior to or on the data cutoff date in the clinical database. It can be the last visit date or last contact date that the patient is known to be alive.

OS will be analyzed and summarized in a same manner as for PFS in Table 9 based on Efficacy Population.

4.6.2.6 CNS Metastases Activity

NSCLC patients' brain tumor lesions will be assessed by RECIST v1.1 (Eisenhauer version 1.1, 2009).

CNS metastases lesion response (CR) is defined as

- disappearance of all target CNS/brain lesion(s), including lesions in brain stem and/or cerebellum identified at baseline, and,
- disappearance of all non-target CNS/brain lesion(s), identified as RECIST 1.1 nontarget lesions at baseline, and
- no identification of new CNS/brain lesion(s).
- CNS metastases lesion response (PR) is defined as
- at least a 30% decrease in the sum of diameters of any CNS/brain lesion(s), identified as RECIST 1.1 target lesions at baseline, and,
- if in the absence of
- unequivocal progression of any non-target CNS/brain lesion(s) identified as RECIST 1.1 nontarget lesions at baseline, or
- the identification of new CNS/brain lesion(s).

CNS metastases progression is defined as either

- at least 20% increase in the sum of diameters of target CNS/brain lesion(s), taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5mm, or,
- unequivocal progression of any CNS/brain lesion(s) identified as RECIST 1.1 nontarget lesions at baseline, or
- the identification of new CNS/brain lesion(s).

CNS metastases SD is defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD for target/non-target CNS/brain lesion(s), taking as reference the smallest sum diameters while on study.

CNS metastases activity analysis of intracranial ORR, BOR, CBR, DCR, and DOR will be summarized for RET-fusion CNS metastases sub-population based on RE, RAMD, and Efficacy Population. The intracranial PFS will be also summarized CNS metastases sub-population based on Efficacy Population.

4.6.3 Analysis of Exploratory Efficacy Endpoints

4.6.3.1 EORTC QLQ-C30

EORTC QLQ-C30 are collected for patients enrolled on or after protocol amendment (PA) 4.1 during Phase 2, which all patients' starting dose will be 400 mg QD. The EORTC QLQ-C30 (version 3.0) is a 30-item questionnaire used to evaluate quality of life, and includes five functional domains (physical (PF), cognitive (CF), role (RF), emotional (EF), and social (SF)), three symptom scales (fatigue (FA), nausea and vomiting (NV), and pain (PA)), a global health status / QoL scale (QL), and six single items (dyspnea (DY), insomnia (SL), appetite loss (AP), constipation (CO), diarrhea (DI), and financial difficulties (FI)). Patients in Phase 2 of the study will complete the EORTC QLQ-C30 on Day 1 of Cycles 1 to 12.

All the scales and single-item measures range in score is from 0 to 100. A high score for a functional scale represents a high/healthy level of functioning, a high score for the global health status represents a high QoL, but a high score for a symptom scale / item represents a high level of symptomatology / problems. Scoring method is outlined in Table 11 and the following paragraphs.

Table 11 Scoring the EORTC QLQ-C30 Version 3.0

	Scale	Number of items	Item range	Version 3.0 Item numbers	Function scales
Global health Status /QoL	**QL**	**2**	**6**	**29, 30**	
Functional Scales					
Physical functioning	PF	5	3	1 to 5	F
Role functioning	RF	2	3	6,7	F
Emotional functioning	EF	4	3	21 to 24	F
Cognitive functioning	CF	2	3	20, 25	F
Social function	SF	2	3	26, 27	F
Symptom scales/items					
Fatigue	FA	3	3	10, 12, 18	
Nausea and vomiting	NV	2	3	14,15	
Pain	PA	2	3	9, 19	
Dyspnea	DY	1	3	8	
Insomnia	SL	1	3	11	
Appetite loss	AP	1	3	13	
Constipation	CO	1	3	16	
Diarrhea	DI	1	3	17	
Financial difficulties	FI	1	3	28	

Raw score (RS) is calculated as the average of item score when at least half of the items are not missing.

After RS is calculated, a linear transformation to 0-100 will be applied to get the score (S) use ranges provided in Table 3.

For functional scales S = (1- (RS-1)/range) x 100

For symptom scales / items and global health status S= ((RS-1)/range) x 100

Summary statistics and change from Baseline to Day 1 of each cycle will be presented for all calculated scores for Efficacy Population prespecified subgroups, defined in Section 3.6.4.

A by-patient listing will be provided for EORTC QLQ-C30.

4.6.3.2 Disease-related symptom, bowel movement history

Disease-related symptoms as reported by bowel movement history are collected only for MTC patients from D1 every cycle from Cycles 1 through 12, and D1 on odd cycles after Cycle 13 during Phase 2, which all patients' starting dose will be 400 mg QD.

Summary and change from baseline in bowel movement history over time will be analyzed only for RET-mutation MTC subgroup.

In addition, the frequency of patients who do not have diarrhea over time will be provided for RET-mutation MTC subgroup.

A by-patient listing of bowel movement history will be provided.

4.6.3.3 CNS Metastases Activity for Other Tumor Types other than NSCLC

The intracranial ORR, BOR, CBR, DCR, and DOR for other tumor types other and NSCLC will be summarized accordingly if applicable.

4.7 SAFETY ANALYSIS

The safety data will be summarized by grouped dose level II for overall Safety Population, and by grouped dose level I for prespecified subgroups defined in Section 3.6.4, unless otherwise specified. The safety analysis is primarily conducted for patients started at 400 mg QD of study drug.

4.7.1 Adverse Events

4.7.1.1 Adjacent Adverse Events

Adjacent Adverse Events (AEs) coded to the same PT will be linked. Events are considered adjacent if, for the same PT, the end date of an episode is the same as, or 1 day before, the start date of the next episode. Once linked the adjacent AE will be reported as one AE as follows:

- The start date of the linked AE is the initial onset date (the start date of the first episode).
- The end date of the linked AE is the end date of the last episode or missing if the last episode is ongoing.
- The initial severity grade of the linked AE is the severity grade of first AE episode.
- The highest severity grade of the linked AE is the highest severity grade of all AE episodes (reported severity).
- The linked AE will be considered as treatment related if at least one episode is treatment related.
- The linked AE will be considered as serious if at least one episode is serious.
- The linked AE will be considered as leading to treatment discontinuation if at least one episode leads to treatment discontinuation (similarly for treatment interruption and treatment reduction).
- The outcome of the linked AE is the outcome of the last episode.
- The AE will be considered as requiring treatment if at least one episode is considered as requiring treatment.

AEs and Serious AEs will be recorded on the CRF from screening visit through 30 days after the last dose of study drug. In addition, SAEs that are assessed as related to study treatment and which occur > 30 days post-treatment will also be reported. All AEs will be coded using the most current version of MedDRA. The severity will be graded per the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) 4.0

A patient experiencing multiple AEs (after adjacent AEs have been linked) under the same PT (SOC) will be counted only once for that PT (SOC) by worst severity. If a patient experiences the same (linked) AE more than once with more than one relationship to study drug, the worst causal relationship to study drug will be given precedence. Any missing severity, causality, or outcome will not be imputed and classified as 'Missing'. Detailed imputation rule for missing AE dates are in Section 7.1.

AEs will be analyzed in terms of treatment-emergent adverse events (TEAEs) which are defined as any (linked) AE that has an onset date during or after administration of the first dose of study drug through 30 days after the last dose of study drug or until a subsequent new anticancer therapy, any event that is considered study drug-related regardless of the start date of the event, or any event that is present at baseline but worsens intensity or is subsequently considered study drug-related by the Investigator.

Adverse Event refers to TEAEs unless otherwise specified throughout this document.

The following tables will be provided (Table 12).

1. AE Summary (including all subsequent items)
    - Any AE
    - Grade 3/4/5 AE
    - Any treatment-related AE
    - Grade 3/4/5 treatment-related AE
    - Any SAE
    - Grade 3/4/5 SAE
    - Any treatment-related SAE
    - Study drug adjustment due to AE
        - Any AE leading to treatment discontinuation
        - Any AE leading to treatment discontinuation due to disease progression
        - Any AE leading to treatment discontinuation excluding disease progression
        - Any AE leading to treatment interruption
        - Any AE leading to treatment reduction
    - Study drug adjustment due to treatment-related AE
        - Any treatment related AE leading to treatment discontinuation
        - Any treatment related AE leading to treatment discontinuation due to disease progression
        - Any treatment related AE leading to treatment discontinuation except disease progression
        - Any treatment related AE leading to treatment interruption
        - Any treatment related AE leading to treatment reduction
    - Death (Grade 5) due to AE
    - Death due to AE related to study drug
    - Patients with treatment related AE by NCI CTCAE grade
    - Patients with SAE by NCI CTCAE grade
2. AE by PT/ by SOC and PT
    1. Treatment-related AE by PT/by SOC and PT
3. SAE by PT/by SOC and PT
4. SAE related to study drug by PT/by SOC and PT
5. Grade $\geq$ 3 AE by PT/by SOC and PT
6. Grade $\geq$ 3 treatment related AE by PT/by SOC and PT
7. AE by PT/by SOC and PT, and NCI CTCAE Grade

8. Treatment related AE by PT/by SOC and PT, and NCI CTCAE Grade
9. SAE by PT/by SOC and PT, and NCI CTCAE Grade
10. Treatment related SAE by PT/by SOC and PT, and NCI CTCAE Grade
11. AE leading to interruption of study drug regardless of causality by PT/ by SOC and PT
12. Treatment related AE leading to interruption of study drug regardless of causality by PT/ by SOC and PT
13. AE leading to reduction of study drug regardless of causality by PT/ by SOC and PT
14. Treatment related AE leading to reduction of study drug regardless of causality by PT/ by SOC and PT
15. AE leading to permanent discontinuation of study drug regardless of causality by PT/ by SOC and PT
16. Treatment related AE leading to permanent discontinuation of study drug regardless of causality by PT/ by SOC and PT

In addition, AEs, SAEs, treatment related AEs, treatment related SAEs will be analyzed by age group, sex, geographic region, weight group and race group, and by PT, SOC/PT, or SOC/PT/CTCAE severity grade for prespecified subgroups if applicable, and “All” patients based on Safety Population.

The AEs, related AEs, SAEs, and related SAEs will be further analyzed across RET alteration status and disease types, i.e., RET-mutation MTC, RET-mutation others, RET-fusion thyroid, RET-fusion NSCLC, RET-fusion others, and “All” for Safety Population.

All AEs will be listed for each treated patient in a by-patient listing. Table 12 summarizes tables for AE data analyses.

Table 12 Summary of Adverse Event analyses

Safety Endpoint	Main	By PT	By SOC and PT	By PT and CTCAE Grade	BY SOC, PT, and CTCAE Grade
	Overall, Subgroups [1]	Overall, Subgroups [1]	Overall, Subgroups [1]	Overall, Subgroups [1]	Overall, Subgroups [1]
Summary Table [4]	X				
AE		X	X	X	X
SAE		X	X	X	X
Grade $\geq$ 3 AE		X	X		
Related AE		X	X	X	X
Related SAE		X	X	X	X
Related Grade $\geq$ 3 AE		X	X		
AE Leading to Permanent Study Treatment Discontinuation		X	X		
Related AE Leading to Permanent Study Treatment Discontinuation		X	X		
Adverse Events Leading to Dose Interruption		X	X		
Related Adverse Events Leading to Dose Interruption		X	X		
Adverse Events Leading to Dose Reduction		X	X		
Related Adverse Events Leading to Dose Reduction		X	X		
AE Leading to Death		X			
Related AE Leading to Death		X			

Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; PT = preferred term; SAE = serious adverse event; SOC = system organ class.
[1] Overall, All Safety Population; Subgroups, prespecified subgroups defined in Section 3.6.4 if applicable.
[2] Overall, All Safety Population; Subgroups patients treated at 400 mg QD.
[3] RET alteration status and disease type subgroups, RET-mutation MTC, RET-mutation others, RET-fusion thyroid, RET-altered thyroid, RET-fusion NSCLC, RET-fusion others, and “All”.
[4] Summary AE will also be analyzed by age group, sex, geographic region, and race group for All Safety Population and RET-mutation MTC patients treated at 400 mg QD if applicable.

Table 12 Summary of Adverse Event Tables (Cont'd)

Safety Endpoint	By PT and Age Group (<65 years, ≥ 65 Years)	By SOC, PT and Age Group (<65 years, ≥ 65 Years)	By PT and Sex (Male, Female)	By SOC and PT, and Sex (Male, Female)	By PT, and Geographic Region (USA, Europe, Asia)	By SOC and PT, and Geographic Region (USA, Europe, Asia)
	Overall, and subgroups [2]	**Overall, and subgroup [2]**	**Overall, and subgroup [2]**	**Overall, and subgroup [2]**	**Overall, and subgroup [2]**	**Overall, and subgroup [2]**
AE	X	X	X	X	X	X
SAE	X	X	X	X	X	X
Grade ≥ 3 AE	X	X	X	X	X	X
Related AE	X	X	X	X	X	X
Related SAE	X	X	X	X	X	X
Related Grade ≥ 3 AE	X	X	X	X	X	X
AE/Related AE Leading to Permanent Study Treatment Discontinuation						
AE/Related AE Leading to Dose Interruption						
AE/Related AE Leading to Dose Reduction						

Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; PT = preferred term; SAE = serious adverse event; SOC = system organ class.
[1] Overall, All Safety Population; Subgroups, prespecified subgroups defined in Section 3.6.4 if applicable.
[2] Overall, All Safety Population; Subgroups patients treated at 400 mg QD.

[3] RET alteration status and disease type subgroups, RET-mutation MTC, RET-mutation others, RET-fusion thyroid, RET-altered thyroid, RET-fusion NSCLC, RET-fusion others, and “All”.
[4] Summary AE will also be analyzed by age group, sex, geographic region, and race group for All Safety Population and RET-mutation MTC patients treated at 400 mg QD if applicable.

Table 12 Summary of Adverse Event Tables (Cont'd)

Safety Endpoint	By PT and Race Group (Asian, White, Others)	By SOC and PT, and Race Group (Asian, White, Others)	By PT and Weight Group (<60 kg, ≥60 kg and ≤75kg, >75kg)	By SOC and PT, and Weight Group (<60 kg, ≥60 kg and ≤75kg, >75kg)	By PT and RET alteration status and disease types [3]	By SOC, PT, and RET alteration status and disease types [3]
	Overall, and subgroup [2]	Overall, and subgroup [2]	Overall, and subgroup [2]	Overall, and subgroup [2]	Overall	Overall
AE	X	X	X	X	X	X
SAE	X	X	X	X	X	X
Grade ≥ 3 AE	X	X	X	X		
Related AE	X	X	X	X	X	X
Related SAE	X	X	X	X	X	X
Related Grade ≥ 3 AE	X	X	X	X		
AE/Related AE Leading to Permanent Study Treatment Discontinuation						
AE/Related AE Leading to Dose Interruption						
AE/Related AE Leading to Dose Reduction						

Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; PT = preferred term; SAE = serious adverse event; SOC = system organ class.
[1] Overall, All Safety Population; Subgroups, prespecified subgroups defined in Section 3.6.4 if applicable.
[2] Overall, All Safety Population; Subgroups patients treated at 400 mg QD.
[3] RET alteration status and disease type subgroups, RET-mutation MTC, RET-mutation others, RET-fusion thyroid, RET-altered thyroid, RET-fusion NSCLC, RET-fusion others, and "All".

[4] Summary AE will also be analyzed by age group, sex, geographic region, weight, and race group for All Safety Population and prespecified subgroup patients treated at 400 mg QD if applicable.

4.7.2 Adverse Event Special Interest

The adverse event special interest (AESI) categories will be defined by groups of selected and relevant PTs. Seven identified AESI categories are tumour lysis syndrome, pneumonia, pneumonitis, hypertension, hepatotoxicity, cases of potential drug-induced liver injury and suspected transmission of an infectious agent by a study treatment.

The number and percentage of patients with AESIs will be summarized by AESI category and PT. In addition, the number and percentage of patients with AESIs will be summarized by AESI category, PT, and NCI CTCAE. Similar analyses for treatment related AESIs will also be provided. Any adjacent AEs are reported as one single AE, see Section 4.7.1.1.

Exploratory time to event analyses for the AESI terms will be provided, respectively. Herein, in this section, an event will be used to represent any one of the five AESIs. The analyses include the following categories.

- time to onset (for AEs of any grades, for AEs of Grade 3 or worse [Grade 3^{+}])
- time to resolution (for AEs of any grades, for AEs of Grade 3^{+})

The time to event analyses will be using KM analysis method and the estimated median with two-sided 95% CI and 25th and 75th percentiles will be provided. The KM will be presented over time in weeks for all Safety Population, prespecified subgroups, defined in Section 3.6.4, based on Safety Population. In addition, the summary analyses for time to events will also be provided.

4.7.2.1 Time to Onset

Time to onset is defined from the treatment start date to the start date of first event (the event onset date – study drug start date + 1). Patients without an event will be censored at the date of last study drug plus 30 days (or the data cutoff if earlier).

The time to onset analyses will examine an event at any grade if there is an event, as well as an event of Grade 3+, respectively.

4.7.2.2 Time to Resolution

Resolution is defined as complete resolution. Resolution is achieved if the outcome is resolved with no sequalae.

Time to resolution is defined as (date of resolution – date of onset of (linked) event + 1). Those events that are not resolved will be censored at the earliest of data cutoff date, end of study date, and death date.

If multiple occurrence of an event with different grades are identified, the one with the highest grade will be included. If multiple occurrence of an event with same grade are identified, the one with the longest duration (of linked event) will be included. If multiple

occurrence of an event with same grade and same duration are identified, the first event will be taken.

Here are some examples,

a patient started a Grade 1 event at Day 3 and continued through Day 5. This patient had a Grade 2 at Day 6 through Day 9. This patient had a Grade 3 at Day 10 and continued through Day 19. This patient then had a Grade 2 at Day 20. Furthermore, the patient had Grade 1 at Day 30 and resolved at Day 40. The time to resolution should be Day 40 – Day 3 + 1.

a patient started a Grade 1 event at Day 3 and continued through Day 5. This patient had a Grade 2 at Day 6 through Day 9. This patient had a Grade 3 at Day 10 and continued through Day 19. This patient then had a Grade 2 at Day 20. Furthermore, the patient had Grade 1 at Day 30 and ongoing till the end of study date, death date, or cutoff date. The patient should be censored at the data cutoff date since the event has not been resolved.

The following AE related analyses will be provided for AESIs (Table 13)

.

Table 13 Summary of AESI analyses

Safety Endpoint	By AESI category and PT	By AESI category and PT	By AESI category, PT, and Age Group	By AESI category, PT, and Sex	By AESI category, PT, and Geographic Region	By AESI category, PT, and Race group	By AESI category, PT and NCI CTCAE
	Overall and Subgroups [1]	RET alteration status and Disease Type(s) [2]	Overall and subgroup [3]	Overall and subgroup [3]	Overall and subgroup [3]	Overall and subgroup [3]	Overall, and subgroup [3]
AE	X	X	X	X	X	X	X
Grade ≥3 AE	X	X					X
SAE	X	X	X	X	X	X	X
Related AE	X	X	X	X	X	X	X
Grade ≥3 Related AE	X	X					X
Related SAE	X	X	X	X	X	X	X
AESI leading to dose discontinuation, interruption, reduction, respectively	X	X					X
Time to Onset (All grades, Grade 3+) [4]	X	X					
Time to Resolution (All grades, Grade 3+)[4]	X	X					
AE Leading to Death	X						
Related AE Leading to Death	X						

[1] Overall, All Safety Population; Subgroups, prespecified subgroups defined in Section 3.6.4 if applicable.

[2] Overall, All Safety Population; prespecified subgroups patients treated at 400 mg QD if applicable.
[3] RET alteration status and disease type subgroups, RET-mutation MTC, RET-mutation others, RET-fusion thyroid, RET-fusion NSCLC, RET-fusion others, and “All”.
[4] Summary AE will also be analyzed by age group, sex, geographic region, and race group for All Safety Population and prespecified subgroup patients treated at 400 mg QD if applicable.

4.7.3 Grouped Adverse Events

Adverse events, for the purpose of analysis, a set of comprehensive definitions comprising Sponsor-defined, standardized MedDRA queries [SMQ], high-level terms [HLTs], and Sponsor-defined AE Grouped Terms [AEGTs] will be used to identify and summarize grouped adverse events by medical concept. The medical concepts include identified and potential risks, if not already considered AESIs, as well as potential class effects and include the following:

- Neutropenia
- Thrombocytopenia
- Anaemia
- Haemorrhage
- Severe Infection with Grade 3+
- QT Prolongation
- Decreased Calcium
- Increased Phosphorus
- Increased Potassium
- Lymphopenia
- Transaminase Elevation

Summary analyses will be presented for grouped adverse events. Time to event analysis will be provided for grouped adverse events similar as the ones for AESI terms. Any adjacent AEs are reported as one single AE, see Section 4.7.1.1.

4.7.4 Serious Adverse Events and Deaths

All serious adverse events (SAEs) must be reported whether they are considered causally related to pralsetinib or protocol procedures. SAEs that are assessed as related to pralsetinib will also be reported even if the occurrence is more than 30 days after the last dose of study drug. Any adjacent AEs are reported as one single AE, see Section 4.7.1.1.

A listing of all AEs for patients who died will be provided specifying the date of death, the cause, and the date of last study treatment dose. On treatment death (from first dose date to last dose date + 30 days) will be clearly marked.

4.7.5 Clinical Laboratory Evaluations

Clinical laboratory values are graded according to NCI CTCAE version 4.0 for applicable parameters except creatinine, which will be graded according to NCI CTCAE version 5.0 to correct the grading error for this specific laboratory test used in CTCAE version 4.0.

The summary and changes from baseline will be presented for hematology, serum chemistry (including coagulation), thyroid test laboratory values based on overall Safety Population, and Safety Population RET-mutation MTC and RET-fusion thyroid, respectively.

Shift tables of laboratory data from baseline to worst grade during treatment will be presented for the following parameters. Patients with baseline and post-baseline assessments available will be included in corresponding parameters. The shift table in maximum CTCAE grades of worst (high) and worst (low) assessment will be presented separately.

- Serum chemistry parameters, activated partial thromboplastin time, alanine aminotransferase (ALT), albumin, alkaline phosphatase (ALP), aspartate aminotransferase (AST), total bilirubin, magnesium, phosphate, potassium, prothrombin time and international normalized ratio, sodium, creatinine, and corrected calcium (mmol/L), which is calculated as total calcium in mmol/L + (0.02×(40 – albumin measured in g/L)).
- Hematology parameters, hemoglobin, leukocytes, lymphocytes (absolute), neutrophils (absolute), platelets.

A Hy's law analysis will be provided. The potential Hy's law quadrant is defined as ALT or AST increases above 3-fold the ULN with concomitant total bilirubin increases above 2-fold the ULN.

Urinalysis will be presented in listing only.

Boxplot of selected laboratory tests (including serum chemistry parameters [ALT, albumin, AST, ALP, total bilirubin, phosphate, sodium, calcium, corrected calcium, potassium], hematology parameters [hemoglobin, leucocytes, neutrophils (absolute), lymphocytes (absolute), platelets], and thyroid-test for thyroid patients [thyroid-stimulating hormone (TSH)]) values will be presented by visit.

A by-patient listing will be provided for each laboratory parameter. All results outside predefined normal ranges, and CTCAE grade will be flagged in the data listings.

4.7.6 Vital Signs

Results for height, weight, body mass index (BMI), systolic and diastolic blood pressure (BP), heart rate, and body temperature will be summarized over time point. Changes over time point in BP, pulse rate, and body temperature from baseline will be summarized based on Safety Population. Boxplot of vital sign values and change from Baseline over time will be presented by visit based on overall Safety Population, and prespecified subgroups based on Safety Population, respectively.

Vital sign assessments will also be provided in a by-patient listing.

4.7.7 Electrocardiograms

Electrocardiogram (ECG) overall interpretation (normal, abnormal not clinically significant [NCS], abnormal clinically significant [CS], and not evaluable [NE]) will be presented for actual values and changes from baseline (expressed as improvement, no change, and deterioration) for overall Safety Population and Safety Population subgroups, RET-mutation MTC and RET-fusion thyroid patients.

All ECG assessments will also be provided in a by-patient listing.

4.7.8 Electrocardiogram Holter Monitor

ECG Holter Monitor data and the correlation between ECG Holter Monitor data and PK will be discussed and analyzed in a separate report.

4.7.9 ECOG Performance Status

The frequency counts of patients in each ECOG performance status score over time point will be summarized.

A by-patient listing for all performance status data will also be provided.

4.7.10 Other Safety Parameters

A by-patient data listing for all pregnancy status, physical exam data will be provided.

4.8 PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSIS

4.8.1 Pharmacokinetic Analysis

All PK and exposure-response analyses specified in the protocol will be discussed and provided in a separate report.

4.8.2 Calcitonin and Carcinoembryonic Antigen Pharmacodynamics

Circulating plasma concentrations of calcitonin and CEA will be collected and analyzed for RET-mutation MTC patients across all doses.

For each patient, the change and percent change from baseline will be calculated at each time point with available plasma at baseline and post-baseline at a certain time point. The change from baseline is defined as the difference between post-baseline and baseline, i.e. post-baseline – baseline, respectively. The percent change from baseline in calcitonin and CEA is defined as 100*(post-baseline – baseline)/baseline.

The change and percent change from baseline will be summarized over time for RET-mutation MTC patients by dose level, respectively.

The Waterfall plots for maximum reduction from baseline, defined as the minimum percent change from baseline in calcitonin and CEA, respectively, will be provided for Safety Population RET-mutation MTC all patients and RET-mutation MTC patients treated at 400 mg QD.

In addition, patients' best biochemical response based on calcitonin and CEA will also be analyzed (Wells, et al. (2012), respectively. The definition for CR, PR, SD, PD, and NE are the following in order.

- Complete response is defined as normalization of serum levels (calcitonin and CEA, respectively) following treatment confirmed at a minimum of 4 weeks later. The normalization of serum levels is defined to have serum values within the normal range. Patients having to have normalized serum levels at two visits, which are at least 4 weeks apart (28 days), are complete responses.
- Partial response is defined as at least 50% decrease from baseline levels maintained over a minimum of 4 weeks.
- Stable disease is defined as the change from baseline should be within (-50%, 50%) and maintained for at least 4 weeks.
- Progressive disease is defined as patients whose change from baseline is more than 50% increase from baseline maintained for at least 4 weeks.
- Not evaluable, other situations that are not included in the above 4 categories.

Biochemical response rate (BRR) is defined as the proportion of patients with a confirmed response (complete response [CR] or partial response [PR] for at least two assessments with at least 28 days apart and no disease progression [PD] in between) before PD and/or other anticancer therapy according to calcitonin or CEA, respectively. BRR and its two-sided 95% CI, which is based on the exact binomial distribution (Clopper-Pearson), will be presented by dose level for calcitonin and CEA, respectively. Patients with normal serum levels at baseline will not be included in BRR analysis.

5. INTERIM ANALYSIS

There is no interim analysis for this study.

6. CHANGES FROM THE PLANNED ANALYSIS

6.1 CHANGES FROM THE PLANNED ANALYSES IN PROTOCOL TO SAP VERSION 1.0

Here is the list for changes from the planned analyses in protocol.

- Efficacy Population is not used in this SAP and analyses since Safety Population is applied for overall population and each pre-specified subgroup. The definition for efficacy population for each pre-specified subgroup is same as the definition based on Safety Population.
- NSCLC patients tested with oncomine diagnostic target test (ODxTT) is added as an ODxTT sub-population in this SAP. RET-fusion positive NSCLC with measurable (target) lesions in CNS/brain patients, including brainstem and cerebellum, and without radiotherapy and radiosurgery 2 months before study drug, will be included into CNS metastases sub-population.

- Patients are grouped based on different grouping rules respectively. For example, the grouped starting dose will be based on patients' starting treatment dose.
- CNS metastases activity analysis is added as an exploratory analysis. The exploratory analysis on medical history, prior or concomitant medication, and time to event for pneumonitis, pneumonia, and hypertension are added, respectively.
- TEAE, related TEAE, SAE, and related SAE will be analyzed by 1) prior PD-1/PD-L1 status for RET-fusion NSCLC patients treated at 400 mg QD, 2) by selected subgroups, RET-fusion NSCLC, MTC, others, and all Safety Population treated at 400 mg QD.

6.2 CHANGES FROM SAP VERSION 1.0 TO SAP VERSION 2.0

- The definition for Efficacy Population is added to the SAP. The Efficacy Population is defined as a subset of the Safety Population who were dosed on or before July 11, 2019. This modification was based on feedback received from FDA to allow enough follow-up time from initial response among responders.
- CNS metastases activity analysis is using only lesions in CNS/brain. The CNS ORR which is based on CNS/brain lesions will be provided. However, the analysis for PFS and DOR which are based on CNS/brain lesions are removed.
- The analysis of DOR across RET alteration status, and tumor types, i.e. RET-fusion NSCLC, RET-fusion PTC, MTC, and others, are added as a supportive analysis.
- Three AESI categories, pneumonia AESI, pneumonitis AESI, and tumor lysis syndrome AESI are added. The additional analyses for the AESIs are defined.
- One grouped term neutropenia, which include neutropenia and neutrophil count decreased, is also added. The analyses for grouped neutropenia will follow the same analysis method for AESIs. The exploratory time to event analyses for a single PT hypertension will also be provided.
- The summary analyses of demographics, medical history, prior and concomitant medication, prior anticancer therapies, dose modification will be provided for the AESIs.
- The laboratory parameter creatinine will be graded with NCI CTCAE version 5.0 to correct the grading error for this specific laboratory test used in CTCAE version version 4.03.

6.3 CHANGES FROM SAP VERSION 2.0 TO SAP VERSION 3.0

- The RET-fusion NSCLC subpopulation and corresponding analyses are removed. RET-fusion NSCLC will not split into different categories based on patients' prior therapy(ies).
- The dose-determing population, and DLT related analyses are removed.

- The prior radioactive iodine (RAI) and prior lenvatinib and/or sorafenib are added as two additional categories in prior antineoplastic therapy for RET-fusion thyroid patients.
- The primary analysis population for MTC has been changed from MTC to RET-mutation MTC. The detailed analyses for RET-mutation MTC has been added for primary analysis, secondary analysis endpoints, and safety analysis endpoints.
- The primary analysis population for PTC has been changed from RET-fusion PTC to RET-fusion thyroid. The detailed analysis for RET-fusion thyroid has been added for primary analysis, secondary analysis endpoints and safety analysis endpoints.
- One grouped term thrombocytopenia, which include thrombocytopenia and platelet count decreased, is added. The analysis for grouped thrombocytopenia will follow the same analysis method for AESIs and grouped neutropenia.
- The mitogen-activated protein kinases pathway expression signature analysis is removed from this version. The detailed analysis was documented in SAP Version 2.0.
- The C634X are combined with other genotypes, such as C609, C611, C618, C620, C630 of RET into cysteine rich domain.
- The summary analyses of circulating plasma concentrations of calcitonin and CEA are added for RET-mutation MTC patients. In addition, the BRR analyses based on calcitonin and CEA are also provided, respectively.
- The history CNS metastases are added into baseline characteristics analysis.
- Grouped anemia are added into grouped AE analysis and time to onset of grouped anemia is also added into time to onset analysis.
- The analysis for bowel movement function is added.
- The description about table/listing/figure formats is removed.

6.4 CHANGES FROM SAP VERSION 3.0 TO SAP VERSION 4.0

- The objectives/endpoints/sample size section has been updated according to PA 13.
- The actual enrollment cutoff date has been removed.
- The primary efficacy endpoint ORR and the secondary efficacy endpoint CBR, DCR, and DOR will be analyzed based on RET-altered Measurable Disease Population. The ORR and DOR will be conducted based on Efficacy Population as sensitivity analysis. Other efficacy endpoints will be based on Efficacy Population.
- The RET-fusion NSCLC subpopulation and corresponding analyses are added back to have comprehensive analysis plan.
- The subgroup, RET-altered thyroid patients, has been added into Section 3.6.4. The safety analyses will also be provided for RET-altered thyroid patients.
- The primary efficacy endpoints by RET gene status (hereditary, sporadic, others) for RET-mutation MTC patients has been added.

- The prior line of therapy has been added into baseline characteristics analysis. The primary analysis endpoint by the prior line of therapy will be provided. The derivation of prior line of therapy is also documented in Appendix.
- The RET gene status for MTC has been added into baseline characteristics analysis. The primary analysis endpoint by RET gene status for RET-mutation MTC will be provided. The derivation of RET gene status is also documented in Appendix.
- The definition of RET-fusion NSCLC CNS metastases population has been updated to include more details. In addition, the RET-fusion NSCLC CNS metastases activity analysis has been moved from Additional Exploratory Analysis to the Secondary Efficacy Analysis. The CNS metastases activity for other tumor types other than NSCLC has been added into Additional Exploratory Analysis section (Section 4.6.3).
- The AESI pneumonia, tumor lysis syndrome has been removed from AESI section. The updated AESI hypertension and new AESI hepatotoxicity have been added.

6.5 CHANGES FROM SAP VERSION 4.0 TO SAP VERSION 5.0

- Number of protocol amendment when EORTC QLQ-C30 was introduced was corrected in section 4.6.3.1
- Clarification added in section 4.6.2.1 on the censoring rules for the start of a new antineoplastic/non protocol treatment for PFS and DOR.
- All AE analyses will be done after adjacent AEs have been linked. Section 4.7.1.1 was updated to provide a more detailed explanation on how linked AEs will be reported.
- The AESI of Pneumonia and tumour lysis syndrome have been added back.
- Time to improvement has been removed from section 4.7.2
- Return to Baseline will no longer be consider when analyzing Time to Resolution/Return to Baseline, therefore the name of the endpoint was also changed to Time to Resolution.
- Data imputation guidelines for new anticancer therapy date imputation have been added in section 7.1.5.

6.6 CHANGES FROM SAP VERSION 5.0 TO SAP VERSION 6.0

- All content from version 5 was migrated to the Roche SAP template from the Blueprint Medicines SAP template
- Blueprint Medicines protocol number has been updated to Roche protocol number throughout the SAP. BLU667-1101 to BO42863.
- Updated sections to reflect the changes made in BO42863 Protocol, v14
- Response Evaluable population in section 2.4 has been updated with a clarification of which RET-fusion Others patients should be excluded
- Added Section 3.6.6 - “Grouping patients by baseline weight”

- The WHODrug version used to code prior and concomitant medication and prior antineoplastic therapy was updated from version WHODrug B3, March 2019 to the most current version of WHODrug (section 4.4)
- The RET-fusion solid tumor other than NSCLC and thyroid population was added to the summary of PFS analyses in section 4.6.2.1.
- The MedDRA version used to code adverse events was updated from version 19.1 to the most current version throughout the document
- Summaries of AEs leading to death and related AEs leading to death have been added to the to the Adverse Event analyses in table 12, see section 4.7.1
- In Section 4.7.2, added two additional AESIs,
  - cases of potential drug-induced liver injury
  - suspected transmission of an infectious agent by a study treatment
- In Section 4.7.3, added eight additional grouped AEs:
  - Hemorrhage
  - Severe Infection with Grade 3+
  - QT Prolongation
  - Decreased Calcium
  - Increased Phosphorus
  - Increased Potassium
  - Lymphopenia
  - Transaminase Elevation
- Deleted list of PTs in sections 4.7.2, 4.7.3 and Appendices
- Section 4.7.5 has been updated to include a Hy's law analysis scatter plot

Additional minor changes have been made throughout to improve clarity and consistency

7. APPENDICES

7.1 DATA IMPUTATION GUIDELINES

No imputation will be made for completely missing date unless otherwise specified.
General imputation rules mentioned below apply to partially missing or impossible dates:

- If the stop date is not missing, and the imputed start date is after the stop date, the start date will be imputed by the stop date
- If the start date is not missing, and the imputed stop date is before the start date, then the imputed stop date will be equal to the start date
- Any imputed dates need to be logical. For example, last dose date should not be later than death date.

When imputation rules in subsequent sections contradicts the general rule, always follow the general rule.

7.1.1 Adverse Event Date Imputation

Follow the general rule specified in Section 7.1.

Incomplete Start Date:

Missing day, month, and year

- No imputation will be made; the corresponding AE will be included.

Missing day and month

- If the year is the **same** as the year of the first dose date, then impute day and month as the day and month of the first dose date
- If the year is **prior to** the year of the first dose date, then impute day and month as 31 Dec
- If the year is **after** the year of the first dose date, then impute day and month as 01 Jan.

Missing day only

- If the month and year are the **same** as those of the first dose date, then impute day as the day of the first dose date
- If either the year of partial date is **before** the year of the first dose date, or the years are the same, but the month of partial date is **before** the month of the first dose date, then impute day as last day of the month
- If either the year of partial date is **after** the year of the first dose date, or the years are the same, but the month of partial date is **after** the month of the first dose date, then impute day as first day of the month.

Incomplete Stop Date:

Missing day, month, and year

- No imputation will be made.

Missing day and month

- If the year is the **same** as the year of the last dose date, then impute day and month as the day and month of the last dose date
- If the year is **prior to** the year of the last dose date, then impute day and month as 31 Dec
- If the year is **after** the year of the last dose date, then impute day and month as 01 Jan.

Missing day only

- If the month and year are the **same** as those of the last dose date, then impute day as the day of the last dose date;

- If either the year of partial date is **not the same as** the year of the last dose date, or the years are the same, but the month of partial date is **not the same as** the month of the last dose date, then impute day as last day of the month.

7.1.2 Concomitant Medication Date Imputation

Follow the general rules specified in Section 7.1 and rules in Section 7.1.1.

7.1.3 Prior Therapies Date Imputation

Follow the general rule specified in Section 7.1.

- For partial start date as month and year are available, then impute day as '01'; e.g., impute partial date of 'DEC2013' as '01DEC2013'.
- For partial start date as year only is available, then impute day and month as '01JAN'; e.g., impute partial date of '2013' as '01JAN2013'.
- For partial end date as month and year are available, then impute day as last day of the month; e.g., impute partial date of 'JUN2013' as '30JUN2013'.
- For end date partial as year only is available, then impute day and month as the last day of the year; e.g., impute partial date of '2013' as '31DEC2013'.

If the imputed starting date is earlier than initial diagnosis date, it should be set as the initial diagnosis date. No overlap between the exposure to prior therapies and study drug will be allowed and any overlap of exposure will be queried at data review stage. The end date of prior therapies will be imputed to first dose date of study drug – 15 if there is overlap due to imputation of partial dates. When there are multiple lines of prior therapies, the end date of prior therapies will be imputed to first dose date of the subsequent line of therapy -1 if there is overlap due to imputation of partial dates. If the end year for one prior therapy is the same as the start year for the next prior therapy, impute Jun 30 and Jul 1 of that year for the end and start days if missing months and days.

7.1.4 Death Date Imputation

- If death date is completely missing, will use latest alive date + 1
- If both month and day are missing, then use the first date (01 JAN) of the year, or latest alive date + 1, whichever is later
- If only day is missing, then use the first day of the month, or latest alive date + 1, whichever is later.

7.1.5 New Anticancer Therapy Date Imputation

If at least one new anticancer therapy is used but the start date of new anticancer therapy is partially missing, the incomplete stop date imputation rule in Section 7.1.1 is used. If the start date of new anticancer therapy is completely missing, the next day of the last dose date (i.e. last dose date + 1 day) will be used by assuming the new anticancer therapy is taken the next day after permanently discontinue pralsetinib.

7.2 DERIVATION OF PRIOR LINE OF SYSTEMIC THERAPY

The number of prior systemic therapy regimen, prior therapy agent name, start/end date, response outcome, progression/relapse date if available, and reasons for discontinuation of an agent will be considered in derivation of prior line of systemic therapy using the following steps.

- Step 1, The start of the prior line of therapy is defined as the first eligible systemic therapy. Systemic therapies are defined based on medical review.
- Step 2, Treatment agent(s) documented by the site as part of the same regimen will be considered as the same line of therapy. Maintenance therapies will be considered as part of the same line of therapy. The maintenance therapies in the derivation includes agents having 1) overlapping/adjacent start/stop dates or 2) date of progression being the same across agents.
- Step 3, Agent(s) with a prior disease progression date documented due to any reasons (for example, disease progression, toxicity, etc.), lead to an increase in the line of therapy. If multiple disease progression dates are documented, an increase of the line of therapy only occurs if dates are not within 7 days of each other.

7.3 DERIVATION OF RET GENE STATUS FOR MTC PATIENTS

The RET gene status for MTC patients will be derived according to the following rules in hierarchical order.

- Step 1, If a patient' ctDNA plasma sample collected at Cycle 1 Day 1 (C1D1) is analyzed and mutation allele fraction in RET gene is available, the patient' RET gene status is assigned based on the rules below accordingly.
    - If any mutation allele fraction in RET gene is $\geq$ 40%, a patient's RET gene status will be "Hereditary".
    - If any mutation allele fraction in RET gene is < 40%, a patient's RET gene status will be "Sporadic".
- Step 2, Among patients whose RET gene status are not assigned from Step 1, if their ctDNA plasma samples collected at C1D1 have been tested and their ctDNA tumor samples collected at Screening visit have also been tested and indicated any mutation found in the RET gene, the patients' RET gene status will be assigned to "Sporadic".
- Step 3, Among patients whose RET gene status are not assigned from Steps 1-2, if patients' MTC disease types in electronic data capture (EDC) prior cancer history thyroid page is not "Unknown", the MTC disease types will be used as patients' RET gene status, "Hereditary" or "Sporadic", respectively.
- Step 4, Among patients whose RET gene status are "Unknown" in Step 3, if patients' RET-mutation is "Positive" from EDC RET mutation status page, and their ctDNA plasma sample data collected at C1D1 is also valid, the patients RET gene

status is sporadic. Otherwise, the RET gene status is ‘Unknown’. The ctDNA plasma sample collected at C1D1 tested with comment of “failure” or “failed” or “sample not hold” will not be considered as valid samples.

7.4 TABLE, LISTING, AND FIGURE FORMAT

In the top left portion of each table/listing, a table/listing number followed by the title of the table/listing will be presented. After the title line, optional sub-title or population information can be presented. Horizontal lines will appear before and after the column heading of the table/listing. Footnotes will be put under the main body of text at the bottom of the page.

The sponsor name, protocol number, programmer user identification, status of the table/listing (i.e. draft or final) and SAS program name will appear bottom left in a string and the page number will appear on the bottom right corner of each table/listing. The date and time of creation of table/listing will appear bottom left under the sponsor name. The source listing number will appear bottom left.

A landscape layout is for both table and listing presentations for post-text tables. A portrait layout is for in text table.

In a listing, in the case that a patient’s record has been continued to the next page, an appropriate identification (e.g. the patient identification number) must be presented at the beginning of that page.

7.5 CONVENTIONS

Unless otherwise specified, in summary tables of continuous variables, the minimum and maximum values will be displayed to the same number of decimal places as the raw data, the mean and median will be presented to one extra decimal place compared to the raw data, and the standard deviation will be displayed to two extra decimal places compared to the raw data. Wherever possible data will be decimal aligned.

Unless otherwise specified frequency tabulations will be presented by number and percentage, where the percentage is presented in parenthesis to 1 decimal place (XX.X%).

P-values, if applicable, will be presented to 3 decimal places. If a p-value is less than 0.05 but is greater than or equal to 0.01, then an asterisk (*) will be added next to this value. If a p-value is less than 0.01 but is greater than or equal to 0.001, then two asterisks (**) will be added next to this value. Finally, if the p-value is less than 0.001 then three asterisks (***) will be added next to this value and it will be presented as <0.001. If the rounded result is a value of 1.000, it will be displayed as >0.999.

Any date information in the listing will use the date9. format, for example, 07MAY2002. In the listing, a unit associated with a variable will be presented only once within parentheses either below or next to that variable in the heading portion. If a parameter has multiple units, each unit will be displayed only once, as applicable.

All tables will have their source listing referenced in a footnote. Listings should be sorted by analysis group, patient and visit and have the source data received by data management referenced in a footnote. All tables and listings will be converted into Microsoft Word documents and collated into two complete documents.

8. SOFTWARE

All summaries and statistical analysis will be generated using SAS version 9.4.

9. TABLES, LISTINGS, AND GRAPHS (TLGS) SHELLS AND PROGRAMMING SPECIFICATIONS

The mock tables, listings and figures and the programming specifications are provided in a separate document.

10. REFERENCES

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