Protocol B7461027

Single-Arm Study of Lorlatinib in Participants with Anaplastic Lymphoma Kinase (ALK)-Positive Non-Small Cell Lung Cancer (NSCLC) Whose Disease Progressed After One Prior Second-Generation ALK Tyrosine Kinase Inhibitor (TKI)

Statistical Analysis Plan (SAP)

Version: **1**

Date: 11 Oct 2019

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APPENDICES

1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1 XX Sep 2019	Original 31 Jul 2019	NA	NA

2. INTRODUCTION

This statistical analysis plan (SAP) provides the detailed methodology for summary and statistical analyses of the data collected in Study B7461027. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment.

The analyses of this study will include all data up to a data cut-off date after End of Trial, defined as 12 calendar months after the "last patient first visit" (LPFV) date in the study.

All summaries and analyses will include all data pertaining to visits/assessments performed up to and including the data cut-off date.

2.1. Study Objectives, Endpoints, and Estimands

Study B7461027 is a post-authorization efficacy study (PAES) requested by EMA in order to obtain additional data on the activity of lorlatinib for the treatment of patients with ALK-positive metastatic non-small-cell lung cancer whose disease has progressed after alectinib or ceritinib as the first ALK tyrosine kinase inhibitor (TKI) therapy.

The study focuses mainly on evaluation of antitumor activity, with analysis of safety data limited to Adverse Events.

Objectives	Estimands	Endpoints
Primary		
• To assess Overall and Intracranial Response Rate of single-agent lorlatinib in participants with advanced ALK-positive NSCLC whose disease has progressed on alectinib or ceritinib as the first ALK tyrosine kinase inhibitor (TKI) therapy	• The primary estimand is the treatment effect of lorlatinib by independent central review (ICR) from time of first dose until progression is met or subsequent anti-cancer therapy is administered for all participants who receive at least one dose of lorlatinib without regard to discontinuation from treatment; all	• Confirmed Objective Tumor Response assessed by Response Evaluation Criteria in Solid Tumor (RECIST) version 1.1 per ICR

	response assessments regardless of gaps in tumor assessments are considered	
Secondary		
• To assess secondary measures of clinical efficacy	• The estimand for Objective Response (OR) by investigator (INV) follows the estimand specified for the primary endpoint except that the treatment effect is based on INV • The estimand for Intracranial (IC) response is the Intracranial treatment effect (ie in brain lesions) of lorlatinib from time of first dose until Intracranial progression is met or subsequent anti-cancer therapy is administered for all participants who receive at least one dose of lorlatinib without regard to discontinuation from treatment; all response assessments regardless of gaps in tumor assessments are considered • The estimand for Time to Tumor Response (TTR) is the treatment effect from the time of first dose to the first date of response that is subsequently confirmed for all participant who are responders to lorlatinib	• Every endpoint assessed by RECIST version 1.1 • Confirmed Objective Tumor Response assessed per INV • Confirmed Intracranial tumor response assessed per ICR/INV • TTR per ICR/INV • DOR per ICR/INV • Duration of Intracranial response (IC-DOR) per ICR/INV • PFS per ICR/INV • TTP per ICR/INV

	• The estimand for Duration of Response (DOR) is the treatment effect from the first date of OR that is subsequently confirmed for all participant who are responders to lorlatinib until progression or death, without regard to discontinuation from treatment unless new anti-cancer therapy is initiated or extended gap in tumor assessment is present prior to progression or death • The estimand for IC-DOR follows the estimand specified for the DOR, but limited to intracranial lesions • The estimand for Progression Free Survival (PFS) is the treatment effect from the time of first dose for all participants who receive at least one dose of lorlatinib until progression or death, without regard to discontinuation from treatment unless new anti-cancer therapy is initiated or an extended gap in tumor assessment is present prior to progression or death • The estimand for Time to Tumor Progression (TTP) is the treatment effect from the time of first dose	

	for all participants who receive at least one dose of lorlatinib until progression, without regard to discontinuation from treatment unless participant dies, new anti-cancer therapy is initiated or extended gap in tumor assessment is present prior to progression	
• To confirm the safety and tolerability of lorlatinib	• The estimand for safety is the incidence of Adverse Events from the time of first dose to 28 days post last dosing date or the date of initiation of a new anti-cancer therapy for all participants who receive at least one dose of Lorlatinib	• Adverse Events as characterized by type, frequency, severity (as graded by National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] v.4.03), seriousness, and relationship to study therapy

2.1.1. Primary Estimand

The primary estimand is the treatment effect of Lorlatinib from the time of first dose until progression is met, death or subsequent anti-cancer therapy is administered regardless of tolerability or duration on treatment. It includes the following 4 attributes:

- Population: Participants with Anaplastic Lymphoma Kinase (ALK)-Positive Non-Small Cell Lung Cancer (NSCLC) Whose Disease Progressed After One Prior Second-Generation ALK Tyrosine Kinase Inhibitor (TKI), as defined by the inclusion and exclusion criteria, and who receive at least one dose of lorlatinib

- Variable: Confirmed Objective Response according to RECIST 1.1 per ICR, defined as CR or PR from the date of first dose until PD, death, or start of new anticancer therapy

- Intercurrent event: All data after the intercurrent event “start of subsequent anti-cancer therapy treatment” will be excluded; non adherence to treatment is not an intercurrent event; assessments are considered regardless of gaps in assessments

- Population-level summary: ORR, ie percentage of participants with confirmed complete response [CR] or confirmed partial response [PR] and associated exact CI

2.1.2. Secondary Estimands

A secondary estimand is the treatment effect of Lorlatinib from the time of first dose until progression is met, death or subsequent anti-cancer therapy is administered regardless of tolerability or duration on treatment. It includes the following 4 attributes:

- Population: Participants with Anaplastic Lymphoma Kinase (ALK)-Positive Non-Small Cell Lung Cancer (NSCLC) Whose Disease Progressed After One Prior Second-Generation ALK Tyrosine Kinase Inhibitor (TKI), as defined by the inclusion and exclusion criteria, and who receive at least one dose of lorlatinib

- Variable: Confirmed Objective Response according to RECIST 1.1 per INV, defined as PR or CR from the date of first dose until PD, death, or start of new anticancer therapy

- Intercurrent event: All data after the intercurrent event "start of subsequent anti-cancer therapy treatment" will be excluded; non adherence to treatment is not an intercurrent event; assessments are considered regardless of gaps in assessments

- Population-level summary: ORR, ie percentage of participants with confirmed complete response [CR] or confirmed partial response [PR] and associated exact CI

A secondary estimand is the durability of treatment effect of Lorlatinib from the time of first response until progression is met, death or subsequent anti-cancer therapy is administered regardless of tolerability or duration on treatment for participants showing a confirmed OR per ICR/INV. It includes the following 4 attributes:

- Population: Participants meeting same criteria of Primary estimand and showing a confirmed OR per ICR/INV

- Variables: DoR /DoR censoring status

- Intercurrent event: All data after the intercurrent event "start of subsequent anti-cancer therapy treatment" will be excluded; non adherence to treatment is not an intercurrent event; assessments are considered regardless of gaps in assessments

- Population-level summary: Kaplan-Meier Median of DOR and associated CI

Another secondary estimand is the intra-cranial treatment effect of Lorlatinib from the time of first dose until intra-cranial progression is met per ICR/INV, death or subsequent anti-cancer therapy is administered regardless of tolerability or duration on treatment. It includes the following 4 attributes:

- Population: Participants meeting same criteria of Primary estimand and having CNS metastases at study entry

- Variable: Confirmed IC-OR according to RECIST 1.1 per ICR/INV, defined as intra cranial PR or CR from the date of first dose until PD, death, or start of new anticancer therapy

- Intercurrent event: All data after the intercurrent event "start of subsequent anti-cancer therapy treatment" will be excluded; non adherence to treatment is not an intercurrent event; assessments are considered regardless of gaps in assessments

- Population-level summary: IC-ORR, ie percentage of participants with confirmed intra-cranial complete response [CR] or confirmed intra-cranial partial response [PR] and associated exact CI

Another secondary estimand is the durability of intra-cranial treatment effect of Lorlatinib from the time of first intra-cranial response until intra-cranial progression is met, death or subsequent anti-cancer therapy is administered regardless of tolerability or duration on treatment for participants showing a confirmed IC-OR per ICR/INV. It includes the following 4 attributes:

- Population: Participants meeting same criteria of Primary estimand, having CNS metastases at study entry and showing a confirmed IC-OR per ICR/INV

- Variable: IC-DOR according to RECIST 1.1 per ICR/INV

- Intercurrent event: All data after the intercurrent events "start of subsequent anti-cancer therapy treatment" or "extended gap in tumor assessment prior to progression or death"; non adherence to treatment is not an intercurrent event; assessments are considered regardless of gaps in assessments

- Population-level summary: Kaplan-Meier Median of IC-DOR and 95% CI

Another secondary estimand is the time to effect of Lorlatinib from the time of first dose until response is met for participants showing a confirmed OR per ICR/INV. It includes the following 4 attributes:

- Population: Participants meeting same criteria of Primary estimand and showing a confirmed OR per ICR/INV

- Variable: Time To Response per ICR/INV

- Intercurrent event: All data after the intercurrent event "start of subsequent anti-cancer therapy treatment" will be excluded; non adherence to treatment is not an intercurrent event; assessments are considered regardless of gaps in assessments

- Population-level summary: median of TTR observed on participants using descriptive statistics

Another secondary estimand is the treatment effect of Lorlatinib from the time of first dose until progression per ICR/INV or death is observed or subsequent anti-cancer therapy is administered regardless of tolerability or duration on treatment. It includes the following 4 attributes:

- Population: Participants meeting same criteria of Primary estimand
- Variable: PFS /PFS censoring status (per ICR/INV)
- Intercurrent event: All data after the intercurrent events "start of subsequent anti-cancer therapy treatment" or "extended gap in tumor assessment prior to progression or death" will be excluded; non adherence to treatment is not an intercurrent event
- Population-level summary: Kaplan-Meier Median of PFS and 95% CI

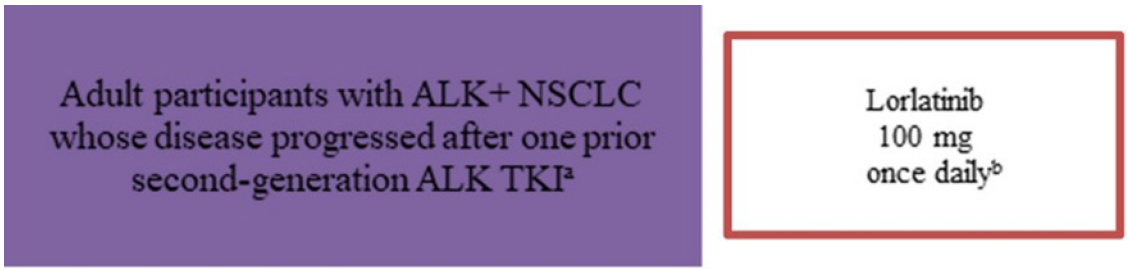
Another secondary estimand is the treatment effect of Lorlatinib from the time of first dose until progression per ICR/INV is observed or subsequent anti-cancer therapy is administered regardless of tolerability or duration on treatment.. It includes the following 4 attributes:

- Population: Participants meeting same criteria of Primary estimand
- Variable: TTP /TTP censoring status (per ICR/INV)
- Intercurrent event: All data after the intercurrent events "start of subsequent anti-cancer therapy treatment" or "extended gap in tumor assessment prior to progression" will be excluded; non adherence to treatment is not an intercurrent event
- Population-level summary: Kaplan-Meier Median of TTP and 95% CI

2.2. Study Design

This is a Phase 4 open-label, multi-center, multi-national, non-randomized, prospective, single arm study of lorlatinib in adult participants with ALK-positive NSCLC who progressed on alectinib or ceritinib as first line of treatment for metastatic disease. Approximately 85 participants will be screened to achieve 70 participants assigned to study intervention.

Participants will take lorlatinib at the approved dose of 100 mg QD. Participants will be treated until disease progression per RECIST 1.1, participant refusal/lost to follow-up, or unacceptable toxicity.



An independent core imaging laboratory will be used in this study for ICR. All sites will be required to submit images for ICR as soon as they are performed at the site so that imaging scans may be read in real time.

After treatment discontinuation participants will be followed for short term follow-up up to 35 days from discontinuation. No long-term follow up will be collected for the study.

The End of Trial is defined as 12 calendar months after the "last patient first visit" (LPFV) date in the study.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint

3.1.1. Confirmed OR by ICR

Objective Response (OR) based on ICR assessment is defined as complete response (CR) or partial response (PR) according to RECIST v1.1 from date of first dose until documented PD or start of new anti-cancer therapy without regard to discontinuation from treatment. Both CR and PR must be confirmed by repeat assessments performed no less than 4 weeks after the criteria for response are first met.
Participants without a CR or PR or with death prior to first post-baseline assessment, inadequate baseline assessment, new anti-cancer therapy started prior to first post-baseline assessment, and all post-baseline disease assessments missing will be considered as non-responders.

3.2. Secondary Endpoints

3.2.1. Confirmed OR by INV

Defined as OR by ICR but evaluated according to INV.

3.2.2. Confirmed IC-OR by ICR/INV

Intra-Cranial Objective Response (OR) based on ICR/derived investigator assessment is defined as Intra-Cranial complete response (CR) or partial response (PR) according to RECIST v1.1 from date of first dose until documented IC-PD or start of new anti-cancer therapy without regard to discontinuation from treatment. Both IC-CR and IC-PR must be confirmed by repeat assessments performed no less than 4 weeks after the criteria for response are first met.
Participants without IC-CR or IC-PR or death prior to first post-baseline assessment,

inadequate baseline assessment, new anti-cancer therapy started prior to first post-baseline assessment, and all post-baseline disease assessments missing will be considered as non-responders.

3.2.3. TTR by ICR/INV

Time to Response (TTR) based on ICR/derived investigator assessments is defined, for participants with a confirmed objective response, as the time from the date of first dose to the first documentation of objective response (CR or PR) which is subsequently confirmed. For participants whose OR proceeds from PR to CR, the onset of PR is taken as the onset of response.

3.2.4. IC-TTR by ICR/INV

Time to Intra-Cranial Response (IC-TTR) based on ICR/derived investigator assessments is defined, for participants with a confirmed intra-cranial objective response, as the time from the date of first dose to the first documentation of objective intra-cranial response (CR or PR) which is subsequently confirmed. For participants whose IC-OR proceeds from PR to CR, the onset of PR is taken as the onset of response.

3.2.5. DoR by ICR/INV

Duration of Response (DoR) based on ICR/ derived investigator assessment is defined, for participants with a confirmed objective response, as the time from first documentation of objective response (CR or PR whichever is earlier) to the date of first documentation of PD or death due to any cause, whichever occurs first. The censoring rules for DOR are identical to those presented for PFS in section 6.2.7.

3.2.6. IC-DoR by ICR/INV

Duration of Intra-Cranial Response (IC-DoR) based on ICR/ derived investigator assessment is defined, for participants with a confirmed objective intra-cranial response, as the time from first documentation of objective intra-cranial response (CR or PR whichever is earlier) to the date of first documentation of PD in brain or death due to any cause, whichever occurs first. The censoring rules for DOR are identical to those presented for PFS in section 6.2.7.

3.2.7. PFS by ICR/INV

Progression Free Survival (PFS) is defined as the time from date of first dose to the date of the first documentation of PD (per RECIST v1.1 based on ICR/derived investigator assessment) or death due to any cause, whichever occurs first. Refer to section 6.2.7 for details on censoring rules.

3.2.8. TTP by ICR/INV

Time To Progression (TTP) is defined as the time from date of first dose to the date of the first documentation of PD (per RECIST v1.1 based on ICR/derived investigator assessment). Refer to section 6.2.8 for details on censoring rules.

3.3. Other Endpoints

Not Applicable

3.4. Baseline Variables

The date of first dose (start date) of study treatment is the earliest date of non-zero dosing of the study drug. The date of last dose of study treatment is the latest date of non-zero dosing of the study drug.

No windowing will be applied when defining baseline, except as noted in Section 5.2.8 for tumor assessments. Any deviations from the protocol specified window will be documented as protocol deviations. A separate definition of adequate baseline will be provided for tumor assessment related efficacy endpoints.

For efficacy analyses and baseline characteristics associated with tumor assessments the last assessment prior to treatment start date will serve as the baseline assessment.

For Adverse Events the last assessment performed on or prior to date of the first dose of study treatment will serve as the baseline assessment. If there are no observations meeting these criteria, then baseline is considered missing.

3.5. Safety Endpoints

Safety endpoints in this study will be limited to Adverse Events and maximum Weight increase from baseline.

3.5.1. Adverse Events

Adverse Events will be summarized based on the on-treatment period unless otherwise specified.

On-treatment is defined as the time from the first dose of study treatment through end of safety follow-up period, ie at least 28 days, and no more than 35 days after discontinuation of treatment, or start of new anti-cancer therapies (follow up systemic therapy, follow up radiation therapy or follow-up surgery), whichever occurs first. Adverse events occurring on the same day as the first dose of study treatment will be considered to have occurred during the on-treatment period.

Adverse events collected outside the on-treatment period as described above will be listed but not summarized. All adverse events with onset date on or after start of a new anti-cancer drug therapy will also be listed on a separate display.

An adverse event is considered treatment emergent (TEAE) when the onset date is greater or equal to the treatment period start date.

All Adverse Events (AEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The investigator will classify the severity of AEs using the CTCAE v4.03.

Adverse Events of Special Interest (AESI)

AESIs include events such as HYPERCHOLESTEROLEMIA and HYPERTRIGLYCERIDEMIA, EDEMA, PERIPHERAL NEUROPATHY, COGNITIVE EFFECTS, MOOD EFFECTS, SPEECH EFFECTS, Weight gain, VISION DISORDER, Liver tests increased, QT interval prolongation, Interstitial lung disease/Pneumonitis, Atrioventricular (AV) block, and Pancreatitis. These events will be defined based on a list of MedDRA Preferred Terms specified in the Safety Review Plan for lorlatinib. A final list will be provided to programming prior to database release.

3.5.2. Vital Signs – Weight

Weight will be summarized based on the on-treatment period.

Assessments of weight which occur on the same day as the first dose of study treatment will be considered baseline assessments (see section 3.4 for the definition of baseline).

4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who sign the ICF
Intent to Treat (ITT)/Safety	All enrolled participants who take at least 1 dose of lorlatinib
Per Protocol Population: Participants with CNS metastases based on ICR	Subset of the ITT analysis set including only participants with CNS metastases at study entry (i.e. with Lesions having Disease Site=Brain) according to ICR
Per Protocol Population: Participants with CNS metastases based on Investigator Assessment	Subset of the ITT analysis set including only participants with CNS metastases at study entry (i.e. with Lesions having Disease Site=Brain) according to Investigator Assessment

Data for all participants will be assessed to determine if participants meet the criteria for inclusion in each analysis population prior to unblinding and releasing the database and classifications will be documented per standard operating procedures.

5. GENERAL METHODOLOGY AND CONVENTIONS

The primary analysis of objective tumor response based on ICR assessment will be performed at study participant data set release after 12 calendar months after the LPFV date in the study (as per End of Trial protocol definition).

Participants who still experience clinical benefit at the End of Trial will discontinue from the study and continue treatment per standard of care.

The study will be reported using CDISC.

5.1. Hypotheses and Decision Rules

5.1.1. Hypotheses and Sample Size

According to literature, platinum-based doublet chemotherapy in participants with ALK + NSCLC refractory to second generation TKIs has an objective response rate of approximately 30%. Setting as target for lorlatinib a response rate of about 43% (as observed in cohort EXP-3B of phase 2 portion of study B7461001), a sample size of 60 participants would result in an exact two-sided 95% CI of the ORR with lower limit of the CI greater than 30%. In order to compensate for a potential 15% drop out rate (participants with death prior to first post-baseline assessment, inadequate baseline assessment, new anti-cancer therapy started prior to first post-baseline assessment, post-baseline disease assessments missing), the overall sample size for the study is set to 70 participants.

5.1.2. Decision Rules

The study will be considered to have met its primary endpoint if the lower limit of the 95% confidence interval around the estimated ORR excludes 30%.

5.2. General Methods

5.2.1. Data handling after the cut-off date

Data after the cut-off date may not undergo the cleaning process and will not be displayed in any listings or used for summary statistics, statistical analyses or imputations

5.2.2. Definition of study day

Start day of study treatment is the day of the first dose of study treatment.

The study day for assessments occurring on or after the first dose of study treatment (eg, adverse event onset) will be calculated as:

Study day = Date of the assessment/event - start date of study treatment + 1.

The study day for assessments occurring prior to the first dose of study treatment (eg, baseline characteristics, medical history) will be negative and calculated as:

Study day = Date of the assessment/event –start date of study treatment.

For efficacy endpoints and for tumor assessment the study day will be calculated with respect to the date of study treatment start.

The study day will be displayed in all relevant data listings.

5.2.3. Definition of Cycle and Cycle Day

Cycle start and end dates are derived per patient. Treatment will be dispensed at the beginning of every 21-day cycle.

- For Cycle X, the actual cycle start date for each subject is the earliest start date of dosing (dose>0 at that visit) in Cycle X visit CRF exposure page
- For all but the last cycle,
  - actual cycle stop date is calculated as the start date of the next cycle minus one day.
  - actual cycle duration is calculated from Day 1 of a cycle to the day prior to Day 1 of the next cycle, as follows: Actual Cycle Duration (weeks) = (cycle stop date – cycle start date + 1) / 7
- For the last cycle, actual cycle duration is calculated as follows:
  - Actual Cycle Duration (weeks) = (last date of study treatment– cycle start date + 1) /7

The cycle day will be calculated as:

- Cycle day = Date of the assessment/event – cycle start date + 1.

5.2.4. Date of last contact

The date of last contact will be derived for patients not known to have died at the data cutoff date using the latest complete date (i.e. imputed dates will not be used in the derivation) among the following:

- All patient assessment dates e.g. tumor assessments
- Start and stop dates of concomitant therapies including non-drug treatments or procedures
- Start and end dates of anti-cancer therapies administered after study treatment discontinuation including systemic therapy, radiation, and surgeries,
- AE start and end dates
- Date of first and last dose
- Vital sign – weight assessment dates
- Date of discontinuation on disposition CRF pages (do not use if reason for discontinuation is lost to follow-up or death).

Only dates associated with actual examinations of the patient will be used in the derivation. Dates associated with a technical operation unrelated to patient status such as the dates data were entered into the CRF will not be used.

Assessment dates after the data cutoff date will not be applied to derive the last contact date.

5.2.5. Measurable Disease

A patient will be considered to have measurable disease if there is at least one target lesion identified at baseline meeting the following criteria:

- Non lymph node lesions with longest diameter ≥ 10 mm by CT scan,
- Non lymph node lesions with longest diameter ≥ 10 mm caliper measurement by clinical exam,
- CNS lesions with longest diameter ≥5 mm provided by gadolinium contrast enhanced MRI perfomed with contingent slices of 1 mm, or
- Lymph nodes with short axis ≥ 15 mm when assessed by CT.

5.2.6. TumorAssessment Date

Tumor assessment dates will be assigned differently for ICR assessment and for investigator's assessment of tumor data.

For analyses of ICR assessments, the date of tumor assessments will be determined based on the radiologist assessments at each nominal timepoint and will be provided on listings as the associated date of response/progression at nominal timepoints. These dates will also be used for censoring in time to event analyses; however, the date of progression and response as provided by ICR will be used in time to event endpoint analyses as the independent oncologist provided an overall assessment of best response and date of progression based on a review of each nominal timepoint and additional clinical information available for the determination of the date of response/progression.

For analyses based on investigator's assessment when response/progression are derived programmatically from the target lesions measurements, non-target lesions status, and new lesions recorded on the CRF, the date of tumor assessment should be derived as the earliest scan/assessment date. Since tumor assessments are captured on a log CRF page, a clustering algorithm for grouping scans will be used:

- Each cluster represents an actual unique assessment date. For each patient, the number of clusters is equal to the maximum number of unique assessment dates available among all target, non-target, new lesions and investigator overall assessment dates. SAS procedure, Proc Fastclus, is applied to a variable that represents the days from the date of treatment start to the date of the scan for each lesion/investigator overall assessment (date of scan – date of treatment start +1). Then the assessments of target and non-target lesions that occurred close to each other in time will be assigned to the same cluster

5.2.7. Sum of Lesion Diameters

For lesions that are assessed as 'too small to measure', 5 mm will be imputed and used in the calculation of the sum of the lesion diameters

5.2.8. Adequate Baseline Tumor Assessment

Adequate baseline is defined using the following criteria:

- All baseline assessments must be within 28 days prior to and including the date of first dose.
- All documented lesions must have non-missing assessments (ie, non missing measurements for target lesions and non missing lesions status at baseline for non-target lesions).
- Measurable disease at baseline (see Section 5.2.5 for the definition of measurable disease)

5.2.9. Adequate Post Baseline Tumor Assessment

An adequate assessment is defined as an assessment where a response of CR, PR, SD, non-CR/non-PD, or PD has been provided by ICR or can be programmatically derived based on investigator's assessment of tumor data for the analyses by ICR or investigator, respectively. Timepoints where the response is not evaluable or no assessment was performed will not be used for determining the censoring date.

5.2.10. Unscheduled Assessments

Unless otherwise specified, unscheduled assessments will not be displayed in summary tables by nominal visit/timepoint. Unscheduled assessments will be used when deriving baseline and worst case on-treatment for Adverse Events. Additionally, unscheduled tumor assessments will be used for efficacy analyses (eg, defining date of progression/censoring, best overall response).

5.2.11. Standard Derivations and Reporting Conventions

The following conversion factors will be used to convert days into weeks, months or years: 1 week = 7 days, 1 month = 30.4375 days, 1 year = 365.25 days.

Percentages will be reported to one decimal place. The rounding will be performed to closest integer / first decimal using the common mid-point between the two consecutive values. Eg,5.1 to 5.4 will be rounded to an integer of 5, and 5.5 to 5.9 will be rounded to an integer of 6.

5.2.12. Analyses for Binary Endpoints

Binary endpoints will be summarized by percentage rates along with two-sided 95% CI using the Clopper-Pearson method (exact CI for a binomial proportion). Waterfall plots will be used to visualize best %change vs baseline in sum of baseline target lesion diameters, Spider plots to visualize %change from baseline in sum of baseline target lesion diameters across visits.

5.2.13. Analyses for Continuous Endpoints

Continuous variables will be summarized using descriptive statistics i.e., number of non-missing values and number of missing values [i.e., n (missing)], mean, median, standard deviation (std), minimum, maximum, first and third quartile (Q1 and Q3), InterQuartile Range.

In case the analysis refers only to certain visits, percentages will be based on the number of participants with an assessment at that visit, unless otherwise specified.

5.2.14. Analyses for Categorical Endpoints

Qualitative variables will be summarized by frequency counts and percentages. Unless otherwise specified, the calculation of proportions will include the missing category. Therefore counts of missing observations will be included in the denominator and presented as a separate category.

In case the analysis refers only to certain visits, percentages will be based on the number of participants with an assessment at that visit, unless otherwise specified.

5.2.15. Analyses for Time-to-Event Endpoints

Time to event endpoints will be summarized using the Kaplan-Meier method and estimated survival curves will be displayed graphically when appropriate. Graphs will describe the number of participants at risk over time. The median, quartiles, and probabilities of an event at particular points in time will be estimated by the Kaplan-Meier method. Confidence intervals for medians and quartiles are based on the Brookmeyer-Crowley method. Confidence intervals for the estimated probability of event at a particular timepoint will be generated using the log(-log) method with back transformation to a confidence interval on the untransformed scale. Summaries of the number and percentages of participants with an event will also be provided on summary tables and figures.

5.3. Methods to Manage Missing Data

Unless otherwise specified, all data will be evaluated as observed, and no imputation method for missing values will be used.

Any imputations will occur at the analysis dataset level. Additionally, in all patient data listings imputed values will be presented and flagged as imputed.

Missing statistics, e.g. when they cannot be calculated, should be presented as ‘ND’ for not done, ‘NR’ for not reached or ‘NA’ for not applicable. For example, if N=1, the measure of variability cannot be computed and should be presented as ‘ND’ or ‘NA’.

5.3.1. Missing Dates

For purposes of data listings, dates will reflect only the information provided by the investigator on the CRF.

If start dates for adverse events or concomitant medications are completely missing, a worst-case approach will be taken whereby the events will be considered treatment emergent and the medications will be considered concomitant. If only partial information is available (e.g. only a month and year or only a year), and the partial information provides sufficient information to indicate the dates are prior to the start of study treatment (e.g. month/year less than month/year of first dose), then these will be considered to have started prior to treatment; otherwise a similar worst case approach will apply and these will be considered to have started after treatment.

Date of Last Dose of Study Treatment

No imputation will be done for first dose date. Date of last dose of study treatment, if unknown or partially unknown, will be imputed as follows:

- If the last date of study treatment is completely missing and there is no End of Treatment (EOT) CRF page and no death date, the participant should be considered to be ongoing and use the data cutoff date for the analysis as the last dosing date; or

- If the last date of study treatment is completely or partially missing and there is EITHER an EOT CRF page OR a death date available (on or prior to the data cutoff date), then impute this date as the last dose date:

  = 31DECYYYY, if only Year is available and Year < Year of min (EOT date, death date),

  = Last day of the month, if both Year and Month are available and Year = Year of min (EOT date, death date) and Month < the month of min (EOT date, death date), or

  = min (EOT date, death date), for all other cases.

Missing or Partial Death Dates

Missing or partial death dates will be imputed based on the last contact date:

- If the entire date is missing it will be imputed as the day after the date of last contact (see derivation of date of last contact in section 5.2.4); or

- If the day or month is missing, death will be imputed to the maximum of the full (non-imputed) day after the date of last contact and the following:

  - Missing day: 1st day of the month and year of death, or
  - Missing day and month: January 1st of the year of death.

Date of Start of New Anti-cancer Therapy

Anti-cancer therapies will be collected in short term follow up only (up to 35 days after treatment discontinuation)

Incomplete dates for new anti-cancer therapy will be imputed as follows and will be used to determine censoring dates for efficacy analyses:

- The end date of new anti-cancer therapy will be included in the imputation for start date of new anti-cancer therapy. If the end data of new anti-cancer therapy is:
    - completely missing then it will be ignored in the imputations below,
    - partially missing with only year available then the imputations below will consider 31DECYYYY as the end date of the new anti-cancer therapy, or
    - partially missing with only month and year available then the imputations below will consider the last day of the month for MMMYYYY as the end date of the new anti-cancer therapy.
- For participants who have not discontinued study treatment at the time of the data cutoff date, last dose of study treatment is set to the data cutoff date in the imputations below.
- If the start date of new anti-cancer therapy is completely or partially missing then the imputed start date of new anti-cancer therapy is:

    = 31DECYYYY, if only Year is available and Year < Year of min [max (PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy]

    = Last day of the month, if both Year and Month are available and

        Year = Year of min [max (PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy]

        Month < Month of min [max (PD date + 1 day, last dose of study treatment + 1 day), end date of new anti-cancer therapy]

    = min [max (PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy], for all other cases.

AE Onset Date

The following imputation rules apply if the event is unique for a participant or it is the first of a series of similar events; otherwise, the AE Onset Date will not be imputed:

- If the AE Collection Date is not missing, is less than the Date of First Exposure to Treatment, and is less than the AE Stop Date, then AE Onset Date is set to the Date of AE Collection.
- If the Previous Visit Date is greater than the Date of First Exposure to Treatment and less than the AE Stop Date, the AE Start Date is set to the previous visit date.

- If the Date of First Exposure to Treatment is greater than the previous visit date and less than the AE Stop Date, the AE Onset Date is set to the Date of First Exposure to Treatment.

- Otherwise AE Onset date is set to the AE Stop date.

AE Stop Date

Ongoing events will have the AE Stop Date set to one of the following values:

- Date of Death, if the participant died and a date of death exists.

- Maximum of (Participant Withdrawal date, AE Onset Date, AE Collection Date) if the participant withdrew from the study and a date of withdrawal exists.

- Maximum of (AE Onset Date, Subject Summary Collection Date, AE Collection Date) if the Subject Summary CRF page exists but a date of withdraw does not exists.

- Maximum of (Last Treatment Date, AE Onset Date) if no Subject Summary page exits.

Imputation will only occur if event is unique for the participant, or it is the last of a series of similar events; otherwise the Stop Date will not be imputed. Adverse Events are deemed similar if they have the same verbatim term.

Resolved events will have the AE Stop Date set to the maximum of the AE collection date and the AE Onset date.

Other Missing or Partial Dates

Imputation methods for other partial dates are as follows:

- If the day of the month is missing for a start date used in a calculation, the first day of the month will be used to replace the missing date.

- If both the day and month are missing, the first day of the year is used.

- For stop dates, the last day of the month, or last day of the year is used if the day or day and month are missing, respectively.

- If the date is completely missing, no imputation will be performed.

5.3.2. Missing Toxicity Grade of Adverse Events

Prior to Study Treatment: If no toxicity grade is available or the grade is reported as unknown for an adverse event prior to the first study treatment, then Grade 1 will be assumed for purposes of defining a baseline grade.

In summaries which present maximum toxicity grade, the maximum of non-missing grades will be displayed. Missing grade will only be displayed for cases where a participant reported only one event and the grade is missing.

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoint

6.1.1. Confirmed OR by ICR

Analysis set: ITT: All enrolled participants who take at least 1 dose of Lorlatinib

Analysis methodology:

- Objective Response Rate (ORR) defined as the percentage of patients with a confirmed best overall response (BOR) of CR or PR according to RECIST v1.1

  BOR will be determined based on reported overall responses at different evaluation timepoints by the independent radiologist from the date of treatment start until documented disease progression or start of new anti-cancer therapy, according to the following rules:

  - CR = at least two determinations of CR at least 4 weeks apart and documented before progression and start of new anti-cancer therapy
  - PR = at least two determinations of PR or better (and not qualifying for a CR) at least 4 weeks apart and before progression and start of new anti-cancer
  - SD (for patients with at least one measurable lesion at baseline) = at least one SD assessment (or better and not qualifying for CR or PR) $\geqslant$ 6 weeks after date of treatment start and before progression and the start of new anti-cancer therapy
  - Non-CR/Non-PD (for patients with only non-target disease at baseline) = at least one Non-CR/Non-PD assessment (or better and not qualifying for CR or PR) $\geqslant$ 6 weeks after date of treatment start and before progression and the start of new anti-cancer therapy
  - PD = progression $\leqslant$ 14 weeks after date of treatment start and not qualifying for CR, PR or SD
  - Not Evaluable (NE) = all other cases.

  Clinical deterioration will not be considered as documented disease progression.

- patients without documented CR or PR will be considered as non-responders
- Exact CI for a binomial proportion for ORR using the Clopper-Pearson method
- best % changes vs baseline as defined below under Summaries used for Reporting

- % change vs baseline across visits as defined below under Summaries used for Reporting

Intercurrent events and missing data:

- data on response after subsequent anti-cancer therapy is administered will be excluded
- participants with death prior to first post-baseline assessment, inadequate baseline assessment, new anti-cancer therapy started prior to first post-baseline assessment, and all post-baseline disease assessments missing will also be considered as non-responders.

Summaries used for reporting:

- The frequency (number and percentage) of patients with BOR of CR, PR, SD, PD, non-CR/non-PD (applicable only to patients with non-measurable disease at baseline), and NE (not-evaluable)
- ORR estimated by dividing the number of patients with OR (CR or PR) by the number of patients in the ITT population
- corresponding exact 2-sided 95% CIs
- Waterfall plots of best %change vs baseline
  A waterfall plot of maximum percent reduction in the sum of longest diameter for non-nodal lesions and short axis for nodal lesions from baseline will be created. These plots will display the best percentage change from baseline in the sum of the diameter of all target lesions for each patient with measurable disease at baseline and at least one valid post-baseline assessment. The best percent change from baseline will be calculated from start of study treatment up to first visit with disease progression or to the last visit available prior to the start of new anti-cancer therapy (for patients who start new anti-tumor therapy prior to progression or who are progression-free patients at the time of analysis)
- Spider Plots of %change from baseline across visits
  A spider plot of %change from baseline across visits in the sum of longest diameter for non-nodal lesions and short axis for nodal lesions from baseline will be presented. These plots will display the % change from baseline in the sum of the diameter of all target lesions for each patient with measurable disease at baseline and at least one valid post-baseline assessment. The % change from baseline will be calculated from start of study treatment to each visit up to first visit with disease progression or to the last visit available prior to the start of new anti-tumor therapy (for patients who start new anti-tumor therapy prior to progression or who are progression-free patients at the time of analysis).

6.2. Secondary Endpoints

6.2.1. Confirmed OR by INV

The primary analysis performed on OR by ICR will be repeated on OR based on INV applying the same rules.

6.2.2. Confirmed IC-OR by ICR/INV

IC-OR by ICR

Analysis set: Participants with CNS metastases based on ICR

IC-OR by INV

Analysis set: Participants with CNS metastases based on Investigator Assessment

Analysis methodology:

The IC-OR, based on ICR/INV, will be summarized similar to OR (as described above in section 6.1 and 6.2), in Per Protocol Population Participants with CNS metastases based on ICR/INV. Surgery or radiotherapy of extracranial lesions will not affect the determination of IC-OR.

6.2.3. TTR by ICR/INV

Analysis set: Subsets of Participants with confirmed objective response by ICR/INV

Analysis methodology: TTR (months) = [first date of CR/PR which is subsequently confirmed-date of first dose+1]/30.4375

For participants whose OR proceeds from PR to CR, the onset of PR is taken as the onset of response.

Intercurrent events and missing data: data on response after subsequent anti-cancer therapy is administered will be excluded.

Summaries used for reporting: TTR will be summarized based on both ICR/INV assessment using simple descriptive statistics (mean, std, median, min, max, Q1, Q3, IQR).

6.2.4. IC-TTR by ICR/INV

Analysis set: Subsets of Participants with confirmed Intra-Cranial objective response by ICR/INV

Analysis methodology: IC-TTR (months) = [first date of CR/PR in brain lesions which is subsequently confirmed-date of first dose+1]/30.4375

For participants whose IC-OR proceeds from PR to CR, the onset of PR is taken as the onset of response.

Intercurrent events and missing data: data on response after subsequent anti-cancer therapy is administered will be excluded.

Summaries used for reporting: IC-TTR will be summarized based on both ICR/INV assessment using simple descriptive statistics (mean, std, median, min, max, Q1, Q3, IQR).

6.2.5. DoR by ICR/INV

Analysis set: Subsets of Participants with confirmed objective response by ICR/INV

Analysis methodology:
DoR will be calculated on every participant showing OR as follows:

DoR (months) = [first date of PD or death/censoring – first date of CR/PR subsequently confirmed+1]/30.4375

Censoring for DOR will be identical to the censoring rules presented for PFS.
Participants with an event more than 14 weeks after the last adequate tumor assessment will be censored on the date of the last adequate tumor assessment prior to the gap that documented no progression. If a new anti-cancer therapy starts prior to an event, the participant will be censored on the date of the last adequate tum or assessment that documented no progression prior to start of the new anti-cancer therapy.

Intercurrent events and missing data: data on response after subsequent anti-cancer therapy is administered will be excluded

Summaries used for reporting: Kaplan-Meier estimates (product-limit estimates) will be presented together with a summary of associated statistics including the median DR time with two-sided 95% CIs. The CIs for the median will be calculated according to Brookmeyer and Crowley.

When the number of participants with PD after a confirmed CR or PR is small, the use of Kaplan-Meier method is limited due to high number of censored observation, so the DOR will be summarized using number (%) of participants with events and of participants censored with DOR in the following categories: less than 6 months, ⩾6 - <9 ,⩾9-<12, ⩾12-<15, ⩾15-<18, ⩾18-<21, ⩾21-<24, and ⩾24 months

6.2.6. IC-DoR by ICR/INV

Analysis set: Subsets of Participants with confirmed Intra-Cranial objective response by ICR/INV

Analysis methodology: IC-DoR (months) = [first date of PD in brain lesions or death/censoring – first date of IC OR (CR/PR subsequently confirmed)+1]/30.4375

For participants whose IC-OR proceeds from PR to CR, the onset of PR is taken as the onset of response.

Censoring for DOR will be identical to the censoring rules presented for PFS.

Intercurrent events and missing data: data on response after subsequent anti-cancer therapy is administered will be excluded.

Summaries used for reporting: The IC-DoR, based on ICR/INV, will be summarized similar to DoR (as described above in section 6.2.5), in Per Protocol Population Participants with CNS metastases based on ICR/INV. Surgery or radiotherapy of extracranial lesions will not affect the determination of IC-OR.

6.2.7. PFS by ICR/INV

Analysis set: ITT: All enrolled participants who take at least 1 dose of Lorlatinib

Analysis methodology:
PFS is defined as the time from date of first dose to the date of the first documentation of PD per RECIST v1.1 as assessed by ICR/INV or death due to any cause, whichever occurs first and will be summarized in months:

PFS (months) = [date of event or censoring–date of treatment start +1]/30.4375.

PFS data will be censored as follows:

- For participants who start a new anti-cancer therapy prior to an event, censoring will be at the last adequate tumor assessment (see Section 5.2.9) prior to the start of new anti-cancer therapy. Note: if date of progression occurs on the same date as the start of new anti-cancer therapy, the progression will be counted as an event.

- For participants with documented progression or death after two or more missing tumor assessments, censoring will occur at the last adequate tumor assessment prior to the missing assessments. In this study antitumor activity will be assessed through radiological tumor assessments conducted at screening and every 6 weeks until disease progression regardless of initiation of subsequent anti-cancer therapy. The allowable time window for disease assessments is ±1week while on treatment and whenever disease progression is suspected (eg, symptomatic deterioration). Therefore time without adequate assessment is defined as 98 days (12 weeks plus 2 weeks).

- For participants who do not have an adequate baseline tumor assessment or who do not have any post-baseline tumor assessments, censoring will occur on the date of first dose unless death occurred on or before the time of the second planned tumor assessment (ie, on or before day 98) in which case the death will be considered an event. Note for participants who died without any post baseline assessments and meet the definition of two or more missing assessment the reason for censoring will be documented as two or more missed assessments and censoring will occur on the date of first dose.

- All other participants alive without objective progression will be censored on the date of the last adequate tumor assessment.

The date of tumor response at each nominal timepoint based on the ICR/INV assessments will be used for determining the dates of last adequate assessment for censoring purposes.

The censoring and event date options to be considered for the PFS analysis are presented in Table 2.

Table 2. Outcome and event dates for PFS analyses

Scenario	Date of event/censoring	Outcome
No adequate baseline assessment	date of first dose	Censored [a]
Progression or death ≤ 98 days after last adequate tumor assessment or ≤ 98 days after date of first dose	Date of progression or death	Event
Progression or death > 98 days after the last adequate tumor assessment [b]	Date of last adequate assessment [b] documenting no PD prior to anti-cancer therapy or missed assessments	Censored
No progression		
New anti-cancer therapy given prior to PD		

[a] if the participant dies ≤ 98 days after date of first dose the death is an event on the death date

[b] if there are no adequate post-baseline assessments prior to PD or death, then the time without adequate assessment should be measured from the date of first dose; if the criteria were met the censoring will be on the start date.

Summaries used for reporting:

Kaplan-Meier estimates (product-limit estimates) will be presented together with a summary of associated statistics including the median PFS time with two-sided 95% CIs. The PFS rate at 12 months will be estimated with corresponding two-sided 95% CIs. The CIs for the median will be calculated according to Brookmeyer and Crowley and the CIs for the survival function estimates at the timepoints defined above will be derived using the log(-log) method according to Kalbfleisch and Prentice (conftype=loglog default option in SAS Proc LIFETEST). The estimate of the standard error will be computed using Greenwood's formula.
Frequency (number and percentage) of participants with each event type (PD or death) and censoring reasons will be presented along with the overall event and censor rates.
Reasons for censoring will be summarized according to the categories in Table 3. If a participant meets multiple definitions for censoring the list will be used to define the hierarchy.

Table 3. Censoring Reasons and Hierarchy for PFS analyses

Hierarchy	Condition	Censoring Reason
1	No adequate baseline assessment	No adequate baseline assessment
2	Start of new anti-cancer therapy before event.	Start of new anti-cancer therapy
3	Event more than 98 days from last adequate post-baseline tumor assessment/start date	Event after missing assessments [a]

4	No event and withdrawal of consent date ≥ start date OR End of study (EOS) = Subject refused further follow-up	Withdrawal of consent
5	No event and lost to follow-up in any disposition page	Lost to follow-up
6	No event and EOS page present and no adequate post-baseline tumor assessment	No adequate post-baseline tumor assessment
7	No event and none of the conditions in the prior hierarchy are met	Ongoing without an event

[a] more than 98 days after last adequate tumor assessment.

The PFS time or censoring time and the reasons for censoring will also be presented in a participant listing.

6.2.8. TTP by ICR/INV

Analysis set: ITT: All enrolled participants who take at least 1 dose of Lorlatinib

Analysis methodology:
TTP is defined as the time from date of first dose to the date of the first documentation of PD per RECIST v1.1 as assessed by ICR/INV and will be summarized in months:

TTP (months) = [date of PD or censoring–date of treatment start +1]/30.4375.

TTP data will be censored as follows:

- For participants who start a new anti-cancer therapy prior to an event, censoring will be at the last adequate tumor assessment (see Section 5.2.9) prior to the start of new anti-cancer therapy. Note: if date of progression occurs on the same date as the start of new anti-cancer therapy, the progression will be counted as an event.

- For participants with documented progression or death after two or more missing tumor assessments, censoring will occur at the last adequate tumor assessment prior to the missing assessments. In this study antitumor activity will be assessed through radiological tumor assessments conducted at screening and every 6 weeks until disease progression regardless of initiation of subsequent anti-cancer therapy. The allowable time window for disease assessments is ±1week while on treatment and whenever disease progression is suspected (eg, symptomatic deterioration). Therefore time without adequate assessment is defined as 98 days (12 weeks plus 2 weeks).

- For participants who do not have an adequate baseline tumor assessment or who do not have any post-baseline tumor assessments, censoring will occur on the date of first dose unless death occurred on or before the time of the second planned tumor assessment (ie, on or before day 98) in which case the death will be considered an event. Note for participants who died without any post baseline assessments and meet the definition of

two or more missing assessment the reason for censoring will be documented as two or more missed assessments and censoring will occur on the date of first dose.

- All other participants alive without objective progression will be censored on the date of the last adequate tumor assessment.

The date of tumor response at each nominal timepoint based on the ICR/INV assessments will be used for determining the dates of last adequate assessment for censoring purposes.

The censoring and event date options to be considered for the TTP analysis are presented in Table 4.

Table 4. Outcome and event dates for TTP analyses

Scenario	Date of event/censoring	Outcome
No adequate baseline assessment	date of first dose	Censored
Progression ≤ 98 days after last adequate tumor assessment or ≤98 days after date of first dose	Date of progression	Event
Death ≤ 98 days after last adequate tumor assessment or ≤ 98 days after date of first dose	Date of death	Censored
Progression or death > 98 days after the last adequate tumor assessment [a]	Date of last adequate assessment [b] documenting no PD prior to anti-cancer therapy or missed assessments	Censored
No progression		
New anti-cancer therapy given prior to PD		

[a] if there are no adequate post-baseline assessments prior to PD or death, then the time without adequate assessment should be measured from the date of first dose; if the criteria were met the censoring will be on the start date.

Summaries used for reporting:

Kaplan-Meier estimates (product-limit estimates) will be presented together with a summary of associated statistics including the median TTP time with two-sided 95% CIs. The TTP rate at 12 months will be estimated with corresponding two-sided 95% CIs. The CIs for the median will be calculated according to Brookmeyer and Crowley and the CIs for the survival function estimates at the timepoints defined above will be derived using the log(-log) method according to Kalbfleisch and Prentice (conftype=loglog default option in SAS Proc LIFETEST). The estimate of the standard error will be computed using Greenwood's formula.
Frequency (number and percentage) of participants with PD and each censoring reasons will be presented along with the overall event and censor rates.
Reasons for censoring will be summarized according to the categories in Table 5. If a participant meets multiple definitions for censoring the list will be used to define the hierarchy.

Table 5. Censoring Reasons and Hierarchy for TTP analysis

Hierarchy	Condition	Censoring Reason
1	No adequate baseline assessment	No adequate baseline assessment
2	Start of new anti-cancer therapy before event.	Start of new anti-cancer therapy
3	Event more than 98 days from last adequate post-baseline tumor assessment/start date	Event after missing assessments [a]
4	No event and withdrawal of consent date ≥ start date OR End of study (EOS) = Subject refused further follow-up	Withdrawal of consent
5	No event and lost to follow-up in any disposition page	Lost to follow-up
6	No event and EOS page present and no adequate post-baseline tumor assessment	No adequate post-baseline tumor assessment
7	No event and Death recorded in any disposition page or Notice of Death	Patient died
8	No event and none of the conditions in the prior hierarchy are met	Ongoing without an event

[a] more than 98 days after last adequate tumor assessment.

The TTP time or censoring time and the reasons for censoring will also be presented in a participant listing.

6.3. Other Endpoint(s)

Not Applicable

6.4. Subset Analyses

Primary endpoint OR by ICR will be reported also by:

- prior ALK inhibitor (Alectinib or Ceritinib)
- prior Chemotherapy (Yes/No)

6.5. Baseline and Other Summaries and Analyses

6.5.1. Baseline Summaries

- **Demographic and Physical Characteristics**

The following demographic and baseline characteristics will be summarized by number and percentage:

- Gender(male, female)
- Age (18-<45; 45- <65; ≥65) .

- Race (white, black, Asian, other)
- Eastern Cooperative Oncology Group (ECOG) Performance status

will be summarized by category (number and percent).

Age (continuous), weight (kg), will be summarized with descriptive statistics (mean, median, standard deviation, minimum, and maximum, inter quartile range).

- **Disease Characteristics**

The following baseline disease characteristics will be summarized by number and percentage according to both ICR/INV:

- Measurable disease at baseline (yes/no) (see section 5.2.5)
- Involved tumor sites at baseline.
- Number of sites of disease at baseline (1, 2, ≥3)

Time since diagnosis (months), defined as (date of first dose – date of diagnosis)/30.4375, will be summarized by descriptive statistics (mean, median, standard deviation, minimum, and maximum).

Involved tumor sites at baseline will be derived from target and non-target lesions at baseline. Each participant will be counted once per organ. Similarly, number of sites of disease at baseline will be derived by counting the number of unique organ sites from target and non-target lesions at baseline. "Other" will be counted as one organ site.

- **Medical History**

Medical history will be coded using the most current version of MedDRA and summarized by MedDRA's System Organ Class (SOC) and PT. Each participant will be counted only once within each PT or SOC. Summaries will be ordered by primary SOC and PT in descending order of frequency. Separate summaries will be provided for past and present conditions.

- **Prior Anti-Cancer Treatments**

Prior anti-cancer treatments include systemic therapy, radiation, and surgery. The number and percentage of participants in each of the following anti-cancer therapy categories will be tabulated:

- Participants with at least one type of prior anti-cancer treatment;
- Participants with at least one prior anti-cancer drug therapy;

- Participants with at least one prior anti-cancer radiotherapy;
- Participants with at least one prior anti-cancer surgery.

Prior anti-cancer drug therapy will be summarized as follows based on the number and percentage of participants:

- Number of prior anti-cancer therapy regimens: missing / 1 / 2 / 3 / ≥4;
- Number of participants who received prior chemotherapy
- Number of participants who received Alectinib/Ceritinib as Prior ALK Inhibitor

The prior anti-cancer drugs will be coded in the WHO Drug coding dictionary.

6.5.2. Study Conduct and Participant Disposition

The study protocol consists of two different epochs: Study and Treatment.

6.5.2.1. Participant Disposition

A summary of the number of participants enrolled by country and site will be provided for the Enrolled population.

Discontinuations from study will be summarized using the Enrolled set.
Discontinuations from study treatment will be summarized using the ITT set

Discontinuations from study treatment due to adverse events will be identified as either related or not related to study treatment. If causality is missing the event will be considered related to treatment. If multiple events lead to study treatment discontinuation and at least one was considered related, discontinuation will be reported as related to study treatment.

An additional summary to meet European Union Disclosure requirements will categorize discontinuations due to adverse events based on the following categories:

- Adverse Event, not serious
- Adverse event, serious non-fatal
- Adverse event, serious fatal

6.5.2.2. Protocol Deviations

Protocol deviations will be compiled prior to database closure and will be summarized by category (n(%)) for the Enrolled Analysis Set. Categories will be assigned by the study Clinician.

6.5.3. Study Treatment Exposure

6.5.3.1. Exposure to lorlatinib

Exposure will be summarized for the ITT/Safety analysis set.

The summary of treatment exposure for lorlatinib will include the following information:

- Treatment duration (days)
- Cumulative dose (mg)
- Dose intensity (mg/day)
- Relative dose intensity (%).

The duration of lorlatinib (in days) is defined as:

Treatment duration (days) = (last dose date – first dose date + 1)

The cumulative dose (mg) of lorlatinib is the sum of the actual dose levels that the participant received (i.e., total dose administered (mg)).

The dose intensity (DI) and the relative dose intensity (RDI) of lorlatinib will be calculated for each participant during the study. The DI (mg/day) of lorlatinib during the study is defined as

DI (mg/day) = [cumulative dose (mg)]/[treatment duration (days)]

The RDI of lorlatinib is defined as the ratio of the DI and planned dose intensity d and expressed in %

RDI (%) = 100× [DI (mg/day]/[d (mg/day)].

6.5.3.2. Dose Reductions and Interruptions

A dose reduction is defined as a non-zero dose that is less than the prior dose.

The number and percentage of participants with at least one dose reduction as well as a breakdown of dose reductions (1 / 2 / 3 / ⩾4) will be summarized.

Reasons for dose reductions will also be summarized. Participants can contribute to more than one reason if multiple dose reductions occurred for different reasons, but will only be counted once per reason. Percentages will be calculated based on the total number of participants in safety analysis set.

An interruption is defined a 0 mg dose administered on one or more days. (Note: A dose interruption is not considered a dose reduction). The number and percentage of participants

with dose interruptions and the corresponding reasons will be summarized. Participants can contribute to more than one reason if multiple dose interruptions occurred for different reasons, but will only be counted once per reason. Percentages will be calculated based on the total number of participants in safety analysis set.

What follows defines how dose interruptions will be counted in the case of multiple dose interruptions:

- If an interruption occurs consecutively for at least two days due to the same reason, then it will be counted only once.
- If an interruption occurs consecutively for at least two days due to different reasons, then it will be counted for each reason.
- If an interruption occurs for more than one day due to the same reason, but the days are not consecutive, i.e. there is at least one dosing day in between, then each dose interruption will be counted as a different occurrence.

6.5.4. Concomitant Medications and Nondrug Treatments

Concomitant medications and non-drug treatments received by participants during the study will be summarized for the Safety Analysis Set.

Concomitant medications refer to all medications which started prior to first dose of study treatment and continued during the on-treatment period (see section 5.2) as well as those started during the on-treatment period. Concomitant medications will be coded in the WHO Drug coding dictionary and will be tabulated by Anatomical Therapeutic Chemical (ATC) Classification level 2 and preferred term in descending order of frequency. In case of equal frequency regarding drug class (respectively drug name), alphabetical order will be used. A participant will be counted only once within a given drug class and within a given drug name, even if he/she received the same medication at different times. Preferred Terms will be reported under each ATC class that it is included under within WHO Drug (no primary path is available in WHO Drug)

Concomitant non-drug treatments refer to all non-drug treatments administered during the on-treatment period. Non-drug treatments will be coded with the most current version of MedDRA and will be summarized by MedDRA's SOC and PT in descending order of frequency.

Participants will be counted only once per PT even if he/she received the same treatment multiple times.

Any medications or non-drug treatments, aside from anti-cancer treatments described in section 6.5.1, which were only administered prior to treatment start will be listed but not summarized.

6.5.5. Subsequent Anti-Cancer Therapies/Procedures

Subsequent Anti-Cancer Therapies and Procedures are defined as therapies entered on the short term follow up in the 'Follow-up Cancer Therapy', 'Follow-up Radiation Therapy', and 'Follow-up Surgery' CRF pages. The number and percentage of participants within each category (medication therapy, radiation therapy, and surgeries) will be provided.

Medications will be coded using the WHO Drug coding dictionary and will be tabulated by preferred term in descending order of frequency.

Analyses will be based on the ITT analysis set.

6.6. Safety Summaries and Analyses

Summaries of AEs and other safety parameters will be based on the Safety analysis set.

6.6.1. Adverse Events

All analyses will be based on treatment emergent events unless otherwise specified. Treatment emergent is defined in section section 3.5.1.

High-level summaries of adverse events (both All Causality and Treatment Related) will include the number and percent of participants with:

- Any Adverse Event;
- Serious AE;
- Adverse Events with CTCAE Grade 3-4;
- Grade 5 events;
- AEs leading to dose interruptions;
- AEs leading to dose reductions;
- AEs leading to withdraw;

Additionally, the number of events reported for each of the categories above will be provided. Each unique adverse event at the PT level for a participant is included in the count.

Seriousness, relatedness, toxicity grade, action taken (interruption, reduction, and withdraw) are as reported by the investigator on the adverse event CRF.

Summaries by System Organ Class and PT in decreasing frequency will be provided for:

- Treatment Emergent Events by Maximum Toxicity Grade (All Causality);
- Treatment Emergent Events by Maximum Toxicity Grade (Treatment Related);

- Serious Treatment Emergent by Maximum Toxicity Grade Events (All Causality);
- Serious Treatment Emergent by Maximum Toxicity Grade Events (Treatment Related);

An event will be considered treatment related if the investigator considered the event related to the study drugs or this information is unknown.

Clustered adverse events will be summarized by maximum CTCAE grade and causality (all-causality and treatment-related) together with other adverse events. Adverse Events pertaining to each cluster will be summarized separately, by cluster. The clustered events are described in a list in the product's Safety Review Plan maintained by the Sponsor.

The following summaries will be provided by PT/Cluster Term (summaries will not include SOC) in decreasing frequency:

- Treatment Emergent Events (All Causality) by Preferred Term and Maximum Toxicity Grade;
- Treatment Emergent Grade 1-2, 3-5 Events (All Causality) by Preferred Term and Maximum Toxicity Grade;
- Treatment Emergent Adverse Events Leading to Dose Interruptions (All Causality);
- Treatment Emergent Adverse Events Leading to Dose Reductions (All Causality);
- Treatment Emergent Adverse Events Leading to Permanent Withdrawal (All Causality);
- Treatment Emergent Adverse Events Leading to Dose Interruptions (Treatment Related);
- Treatment Emergent Adverse Events Leading to Dose Reductions (Treatment Related);
- Treatment Emergent Adverse Events Leading to Permanent Withdrawal (Treatment Related);
- Serious Treatment Emergent Events (All Causality).
- Serious Treatment Emergent Events (Treatment Related).

Each participant will be counted only once within each SOC, Cluster Term and PT.

As described in section 5.3, in case a participant has events with missing and non missing toxicity grades, the maximum of the non-missing grade will be displayed. Missing grade will only be displayed in the event that only one event has been reported for a participant and the grade is missing.

6.6.1.1. Basic Results

For summaries required for basic results disclosures in the US and EU the follow additional summaries will be provided:

- Treatment Emergent Non-Serious Adverse Events by SOC and PT in >5% of participants;
- Treatment Emergent Non-Serious Adverse Events by SOC and PT;
- Treatment Emergent Serious Adverse Events by SOC and PT; and
- Fatal Adverse Events by SOC and PT.

Each of the above summaries will include a count of the number of participants with all causality events and the number of participants with treatment related events.

6.6.1.2. Adverse Events of Special Interest

These analyses will be performed for treatment emergent AEs of special interest as specified in 3.5.1:

- Treatment Emergent Events by Maximum Toxicity Grade (All Causality);
- Treatment Emergent Events by Maximum Toxicity Grade (Treatment Related);

6.6.2. Deaths

The frequency (number and percentage) of participants in the safety analysis set who died and who died within 28 days after last dose of study treatment as well as the primary reason for death, will be tabulated based on information from the 'Notice of Death'.

The frequency (number and percentage) of participants in the safety analysis set who died within 30 days of first dose of study treatment will also be provided.

Date and cause of death will be provided in individual participant data listing together with selected dosing information (date of first / last administration, dose).

6.6.3. Vital Signs – Weight

The number and percent of patients in each of the following maximum body weight categories will be presented:

- Maximum change from baseline body weight (increase) $< 10\%$
- Maximum change from baseline body weight (increase) $\geq 10\%$ and $< 20\%$
- Maximum change from baseline body weight (increase) $\geq 20\%$

7. INTERIM ANALYSES

7.1. Introduction

Not applicable

7.2. Interim Analyses and Summaries

Not applicable

8. APPENDICES

Appendix 1. List of Abbreviations

Abbreviation	Term
AE	adverse event
AESI	adverse event of special interest
BOR	best overall response
CDARS	Clinical Data Analysis and Reporting System (of US Food and Drug Administration)
CDISC	Clinical Data Interchange Standards Consortium
CI	confidence interval
CR	complete response
CRF	case report form
CTC	common toxicity criteria
DoR	duration of response
ECOG	Eastern Cooperative Oncology Group
EOT	End of Treatment
ICF	informed consent form
ICR	independent central review
ITT	intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
NA	Not Applicable
ND	Not Done
NR	Not Reached
OR	Objective Response
ORR	Overall Response Rate
PD	progressive disease/disease progression
PFS	Progression Free Survival
PR	Partial Response
PT	preferred term
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SAP	statistical analysis plan
std	standard deviation
SD	Stable Disease
SOC	system organ class
TTR	time to response
TEAE	Treatment Emergent Adverse Event
WHO	World Health Organization