**Protocol B7461030**

# SINGLE-ARM STUDY TO EVALUATE THE SAFETY OF LORLATINIB IN ALK INHIBITOR-TREATED UNRESECTABLE ADVANCED AND/OR RECURRENT ALK-POSITIVE NON-SMALL CELL LUNG CANCER PARTICIPANTS IN INDIA

**Statistical Analysis Plan**
**(SAP)**

**Version:** **1**

**Date:** 03 June 2020

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## 1. VERSION HISTORY

This Statistical Analysis Plan (SAP) for study B7461030 is based on the protocol version 1 dated 30Mar2020.

**Table 1. Summary of Changes**

| Version/ Date | Associated Protocol Amendment | Rationale | Specific Changes |
|---|---|---|---|
| 1/ 03 June 2020 | Original 30 March 2020 | N/A | N/A |

## 2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in Study B7461030. 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.

Any deviations from this analysis plan will be described in the Clinical Study Report.

All summaries and analyses will include all data in the database at the end of the study which is defined as 1 year after the last participant first visit date in the study.

## 2.1. Study Objectives, Endpoints, and Estimands

| Objective | Estimands | Endpoints |
|---|---|---|
| **Primary** | | |
| • To evaluate the safety and tolerability of single-agent lorlatinib in participants with unresectable advanced and/or recurrent ALK-positive Non-Small Cell Lung Cancer (NSCLC) with resistance or intolerance to at least 1 prior ALK inhibitor treatment. | • The primary estimand is the incidence of Adverse Events (AEs) from the time of first dose to at most 35 days post last dosing date or the date of initiation of a new anticancer therapy for all participants who receive at least 1 dose of lorlatinib, regardless of dosing interruptions or dosing compliance. | • Incidence of AEs. |
| **Secondary** | | |
| • To evaluate overall and intracranial antitumor activity of single-agent lorlatinib in participants with unresectable advanced and/or recurrent ALK-positive NSCLC with resistance or intolerance to at least 1 prior ALK inhibitor treatment. | • The secondary estimand is the treatment effect of lorlatinib as assessed by the investigator from time of first dose (Objective Response Rate (ORR) and Intra Cranial-Objective Response Rate (IC-ORR)) or time of first response (Duration of Response (DoR) and Intracranial Duration of Response (IC-DoR)) until progression is met, death or subsequent anticancer therapy is administered for all participants who receive at least 1 dose of lorlatinib without regard to tolerability or discontinuation from treatment. | • Confirmed ORR, confirmed IC-ORR, DoR and IC-DoR as assessed by the Investigator using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. |

### 2.1.1. Primary Estimand

The primary estimand is the incidence of Adverse Events from the time of first dose to 35 days post last dosing date or the date prior to initiation of a new anticancer therapy, whichever occurs first for all participants who receive at least one dose of lorlatinib, regardless of dosing interruptions or dosing compliance. It includes the following 4 attributes:

- Population: Participants with unresectable advanced and/or recurrent ALK-positive NSCLC with resistance or intolerance to at least 1 prior ALK inhibitor treatment as defined by the inclusion and exclusion criteria, and who receive at least one dose of Lorlatinib

- Variable: Binary indicator of whether any AE occurring at least once

- Intercurrent event: All data after the intercurrent event "initiation of a new anticancer therapy (-1 day)" or "treatment discontinuation (+35 days post last dosing date)" will be excluded. Dosing interruptions or dosing compliance are not considered as intercurrent event for this analysis..

- Population-level summary: Adverse event incidence rate from the time of first dose to 35 days post last dosing date or the date prior to initiation of a new anticancer therapy, whichever occurs first. AE incidence rate is the number of patients with any AE occurring at least once in the study population.

### 2.1.2. Secondary Estimands

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

- Population: Participants with unresectable advanced and/or recurrent ALK-positive NSCLC with resistance or intolerance to at least 1 prior ALK inhibitor treatment as defined by the inclusion and exclusion criteria, and who receive at least one dose of lorlatinib

- Variable: Confirmed Objective Response (OR) according to RECIST 1.1 per investigator, defined as confirmed partial response (PR) or confirmed complete response (CR) from the date of first dose until progressive disease (PD), death, or start of new anticancer therapy

- Intercurrent event: All data after the intercurrent event "start of subsequent anticancer therapy" will be excluded. All tumor assessments are considered regardless of gaps in assessments. Treatment interruptions is not an intercurrent event.

- Population-level summary: ORR, ie percentage of participants with confirmed CR or confirmed PR and corresponding 95% confidence interval (CI) based on Wilson's Score Method.

Another secondary estimand is the durability of treatment effect of Lorlatinib as assessed by the investigator from the time of first response until progression is met, death or subsequent anticancer therapy is administered regardless of tolerability or duration on treatment for participants showing a confirmed OR per investigator. It includes the following 4 attributes:

- Population: Participants with unresectable advanced and/or recurrent ALK-positive NSCLC with resistance or intolerance to at least 1 prior ALK inhibitor treatment as defined by the inclusion and exclusion criteria, who receive at least one dose of lorlatinib and showing a confirmed OR per investigator

- Variables: DoR

- Intercurrent event: All data after the intercurrent events "start of subsequent anticancer therapy" or "extended gap in tumor assessment prior to progression or death" will be excluded. Treatment interruptions is not an intercurrent event.

- Population-level summary: Kaplan-Meier Median of DoR and 2-sided 95% CI

Another secondary estimand is the intracranial treatment effect of Lorlatinib as assessed by the investigator from the time of first dose until intracranial progression is met per investigator, death or subsequent anticancer therapy is administered regardless of tolerability or duration on treatment. It includes the following 4 attributes:

- Population: Participants with unresectable advanced and/or recurrent ALK-positive NSCLC with resistance or intolerance to at least 1 prior ALK inhibitor treatment as defined by the inclusion and exclusion criteria, who receive at least one dose of lorlatinib and having Central Nervous System (CNS) metastases at study entry

- Variable: Confirmed Intracranial-Objective Response (IC-OR) according to RECIST 1.1 per investigator, defined as confirmed Intracranial Partial Response (IC-PR) or Intracranial Complete Reponse (IC-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 anticancer therapy" will be excluded. All tumor assessments are considered regardless of gaps in assessments. Treatment interruptions is not an intercurrent event.

- Population-level summary: IC-ORR, ie percentage of participants with confirmed IC-CR or confirmed IC-PR and corresponding 95% confidence interval based on Wilson's Score Method.

Another secondary estimand is the durability of intracranial treatment effect of Lorlatinib as assessed by the investigator from the time of first intracranial response until intracranial progression is met, death or subsequent anticancer therapy is administered regardless of tolerability or duration on treatment for participants showing a confirmed IC-OR per investigator. It includes the following 4 attributes:

- Population: Participants with unresectable advanced and/or recurrent ALK-positive NSCLC with resistance or intolerance to at least 1 prior ALK inhibitor treatment as defined by the inclusion and exclusion criteria, who receive at least one dose of lorlatinib, having CNS metastases at study entry and showing a confirmed IC-OR per investigator

- Variable: IC-DoR according to RECIST 1.1 per investigator

- Intercurrent event: All data after the intercurrent events "start of subsequent anticancer therapy" or "extended gap in tumor assessment prior to progression or death" will be excluded. Treatment interruptions is not an intercurrent event.

- Population-level summary: Kaplan-Meier Median of IC-DoR and 2-sided 95% CI

### 2.1.3. Additional Estimand

Not applicable.

## 2.2. Study Design

This is a Phase 4, open-label, multicenter, non-randomized, prospective, single arm study to evaluate the safety and tolerability of lorlatinib in adult participants with unresectable advanced and/or recurrent ALK-positive NSCLC with resistance or intolerance to at least 1 prior ALK inhibitor treatment.

This study will enroll enough participants to ensure that 100 participants are treated with lorlatinib.

Participants will continue with the assigned study treatment until disease progression, participant refusal/lost to follow-up, or unacceptable toxicity. At the end of the study, participants who are on treatment and benefiting from Lorlatinib treatment will be moved to commercially available Lorlatinib (if considered appropriate by the Investigator) as soon as feasible.

# 3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

## 3.1. Primary Endpoint

The primary endpoint is the incidence of AEs. AEs will be graded by the Investigator according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03 and coded using the Medical Dictionary for Regulatory Activities (MedDRA). The focus of AE summaries will be on treatment-emergent adverse events (TEAEs) defined in section 3.5.1.

## 3.2. Secondary Endpoints

### 3.2.1. Confirmed Objective Response Rate (ORR)

Objective Response (OR) based on investigator assessment is defined as CR or PR according to RECIST v1.1 from date of first dose until documented PD or start of new anticancer 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 anticancer therapy started prior to first post-baseline assessment, and all post-baseline disease assessments missing will be considered as non-responders.

ORR is defined as the percent of participants with best overall response (BOR) as confirmed CR or confirmed PR according to RECIST version 1.1 BOR is defined in section 6.2.1.

### 3.2.2. Confirmed Intracranial Objective Response Rate (IC-ORR)

Intracranial OR based on investigator assessment is defined as IC-CR or IC-PR according to RECIST v1.1 from date of first dose until documented Intracranial Progressive Disease (IC-PD) or start of new anticancer 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 with death prior to first post-baseline assessment, inadequate baseline assessment, new anticancer therapy started prior to first post-baseline assessment, and all post-baseline disease assessments missing will be considered as non-responders.

IC-ORR is defined as the percent of participants with intracranial response (ie, best overall intracranial response as confirmed CR or confirmed PR considering only intracranial lesions) relative to participants with CNS metastases at study entry.

### 3.2.3. Duration of Response (DoR)

DoR is defined as the time from the first documentation of objective tumor response (confirmed CR or confirmed PR) to the first documentation of disease progression or death due to any cause, whichever occurs first. The censoring rules for DOR are presented in section 6.2.3.

### 3.2.4. Intracranial Duration of Response (IC-DoR)

IC-DoR is defined as the time from the first documentation of an intracranial objective response in the subgroup of participants with brain metastasis at baseline. The censoring rules for DoR will be used for IC-DoR.

## 3.3. Other Endpoint

Not applicable.

## 3.4. Baseline Variables

**Start and end dates of study treatment:**

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.

**Definition of baseline:**

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 antitumor activity endpoints.

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

For safety (including laboratory, vital signs and Eastern Cooperative Oncology Group (ECOG) performance status) 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.

Participants who start treatment and discontinue from the study on the same day may have two different sets of data collected on study day 1 (one during study and one in the End of Treatment (EOT) visit. Data reported at the EOT visit are not eligible for baseline selection.

Triplicate electrocardiograms (ECGs) are collected pre-dose; therefore, the baseline for each ECG measurement is the average of the latest pre-dose triplicate measurements. Unscheduled assessments will not be included in the calculation of the average.

### 3.5. Safety Endpoints

Safety endpoints will be summarized based on the on-treatment period unless otherwise specified. Safety data collected outside the on-treatment period as described below will be listed but not summarized.

#### 3.5.1. Treatment Exposure

On-treatment is defined as the time from the first dose of study treatment through end of safety follow-up period, ie 35 days after discontinuation of treatment, or start of new anticancer therapies (follow-up systemic therapy, follow-up radiation therapy to target or non-target lesions or follow-up surgery to target or non-target lesions), 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.

An adverse event is considered treatment emergent (TEAE) if:

- the event occurs for the first time during the effective duration of study treatment and was not observed prior to the start of study treatment (e.g., during screening), or
- the event was observed prior to the start of study treatment but increased in severity during the effective duration of study treatment.

#### 3.5.2. Adverse Event of Special Interest (AESI)

AESIs include events such as CNS (mood, speech, cognition) events. These events will be defined based on a list of MedDRA Preferred Terms (PTs) specified in the Safety Review Plan for lorlatinib. A final list will be provided to programming prior to database release.

#### 3.5.3. Laboratory Data

Hematology, chemistry, and lipids results will be programmatically graded according to the NCI CTCAE version 4.03 for relevant parameters. A shift summary of baseline grade by maximum post-baseline grade will be presented. Parameters which cannot be graded will be summarized relative to the normal range (ie, normal range high or normal range low). Additional details are provided in Section 6.6.1.

#### 3.5.4. Vital Signs

Vital signs data will be summarized using descriptive statistics (mean, standard deviation (Std Dev), median, quartiles, minimum, and maximum) of actual values and change from

baseline for each nominal visit over time (ie, unscheduled assessments will be excluded). Additional details are provided in Section 6.6.2.

### 3.5.5. ECG

Descriptive statistics (n, mean, median, Std Dev, minimum, and maximum) of corrected QT (QTc) and other ECG parameters will be used to summarize absolute values and changes from baseline on treatment. Categorical analysis will be conducted for the maximum change from baseline in QTc, PR, and QRS and the maximum post-baseline QTc interval. Additional details are provided in Section 6.6.3.

## 4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

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

Only participants who signed informed consent will be included in the analysis sets below.

| Population | Description |
|---|---|
| Enrolled | All participants who sign the informed consent document. |
| Safety | All participants who receive at least 1 dose of lorlatinib. |

## 5. GENERAL METHODOLOGY AND CONVENTIONS

All analyses will be performed at study participant data set release at the end of study, defined as 1 year after the last participant first visit (LPFV) date in the study.

### 5.1. Hypotheses and Decision Rules

### 5.1.1. Hypotheses and Sample Size

The primary objective of the study is to evaluate the safety and tolerability of single-agent lorlatinib in participants with unresectable advanced and/or recurrent ALK-positive NSCLC with resistance or intolerance to at least 1 prior ALK inhibitor treatment. No formal statistical hypothesis testing is planned for the primary objective.

This study will enroll enough participants to ensure that 100 participants are treated with lorlatinib.

### 5.1.2. Decision Rules

There is no decision rule for the primary objective.

### 5.2. General Methods

### 5.2.1. 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 (e.g., adverse event onset, tumor measurement) 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 (e.g., baseline characteristics, medical history) will be negative and calculated as:

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

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

### 5.2.2. Definition of Cycle and Cycle Day

Cycle start and end dates are derived per participant. Treatment will be dispensed at the beginning of every 28-day cycle.

- For Cycle X, the actual cycle start date for each participant is:
    - the earliest start date of dosing (dose>0 at that visit) in Cycle X visit Case Report Form (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.

### 5.2.3. Definition of Start of New Anticancer therapy

Start date of new anticancer therapy (drug, radiation, surgery) is used for definition of on-treatment in safety analyses (see Section 3.5.1) and for censoring in antitumor activity analyses (see Section 6.2.3).

The start date of new anticancer therapy is the earliest date after first dose of Lorlatinib amongst the following:

- Start date of anticancer drug therapy recorded in the ‘Concomitant Medications’ CRF pages with ‘Category of medication’ = ‘Follow-up Cancer Therapy’

- Start date of radiation therapy recorded in 'Radiation Treatment' CRF page with 'Subcategory' = 'Curative in intent'

- Surgery date recorded in 'Non-drug Treatments' CRF pages with 'Category' = 'Cancer Surgery' and 'Outcome of Procedure' = 'Resected' or 'Partially Resected'.

When start date of anticancer therapy is missing or partially missing, the imputation rules described in Section 5.3.2.4 should be applied using 'Concomitant Medications', 'Radiation Treatment', and 'Non-drug Treatments' CRF pages.

### 5.2.4. Date of Last Contact

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

- All participant assessment dates e.g. tumor assessments,

- Start and stop dates of concomitant therapies including non-drug treatments or procedures,

- Start and end dates of anticancer 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, ECG, laboratory and 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 participant will be used in the derivation.

### 5.2.5. Measurable Disease

A participant 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 Computerized Tomography (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 Magnetic Resonance Imaging (MRI) performed with contingent slices of 1 mm, or

- Lymph nodes with short axis ≥ 15 mm when assessed by CT.

### 5.2.6. Tumor Assessment Date

The Date of Tumor Assessment at each nominal timepoint as provided by the investigator on the Investigator Overall Tumor Assessment (IOTA) CRF will be utilized for the respective analyses.

### 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 35 days prior to and including the date of first dose.
- All documented lesions must have non-missing assessments (i.e. 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, Stable Disease (SD), non-CR/non-PD, or PD has been provided by the investigator. Timepoints where the response is not evaluable, or no assessment was performed will not be used for determining the censoring date.

### 5.2.10. Nominal and Unscheduled Visits

For all algorithms and analyses, visit labels as specified on the CRF will be used as the nominal timepoint (i.e. assessment will not be slotted).

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 laboratories and vital signs assessments. Additionally, unscheduled tumor assessments will be used for antitumor activity analyses (e.g. defining date of progression/censoring, best overall response, date of last contact).

### 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.

Demographics and physical measurements:

- Age [years]:

- (year of given informed consent - year of birth)

For reporting conventions, mean and median should generally be displayed one more decimal place than the raw data and Std Dev should be displayed to two more decimal places than the raw data. 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 Continuous and Qualitative Variables

Continuous variables will be summarized using descriptive statistics ie, number of non-missing values and number of missing values [ie, n (missing)], mean, median, Std Dev, minimum, maximum, first and third quartile (Q1 and Q3) and inter-quartile range.

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.

### 5.2.13. 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. 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 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 ECG Data

For QTc analyses, no values will be imputed for missing data.

For pre-dose measurements, if one or two of the triplicate measurements for an ECG parameter are missed, the average of the remaining two measurements or the single

measurement can be used in the analyses. If all triplicate measurements are missing at a timepoint for an ECG parameter, no values will be imputed. If the triplicate needs to be repeated because of an artifact, then the repeated triplicate will be reported on an unscheduled CRF page. Based on a review of the data these unscheduled assessments may be used in place of the assessments for pre-dose. Data review and consultation with the study team is required to flag these cases.

### 5.3.2. Handling of Incomplete or Missing Dates

#### 5.3.2.1. Adverse Events

**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 Onset 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 (Withdraw date, AE Onset Date, AE Collection Date) if the participant withdrew from the study and a date of withdraw 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.

#### 5.3.2.2. Exposure

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 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.

#### 5.3.2.3. Date of Death

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

- If the date is missing it will be imputed as the day after the date of last contact
- If the day or both day and 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
  - Missing day and month: January 1st of the year of death

#### 5.3.2.4. Date of Start of New Anticancer Therapy

Incomplete dates for start date of new anticancer therapy (drug therapy, radiation, surgery) will be imputed as follows and will be used for determining censoring dates for antitumor activity analyses and in the derivation of the end of on-treatment period. PD date below refers to PD date by investigator assessment.

- The end date of new anticancer therapy will be included in the imputations for start date of new anticancer therapy. If the end date of new anticancer therapy is
  - completely missing then it will be ignored in the imputations below
  - partially missing with only year (YYYY) available then the imputations below will consider 31DECYYYY as the end date of the new anticancer therapy
  - 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 anticancer therapy

- For participants who have not discontinued study treatment at the analysis cutoff date, last dose of study treatment is set to the analysis cutoff date in the imputations below.
- If the start date of new anticancer therapy is completely or partially missing, then the imputed start date of new anticancer therapy is derived as follows:
  - Start date of new anticancer therapy is completely missing

    Imputed start date = min [max(PD date + 1, last dose of study treatment + 1), end date of new anticancer therapy]
  - Only year (YYYY) for start of anticancer therapy is available

    IF YYYY < Year of min [max(PD date + 1, last dose of study treatment + 1), end date of new anticancer therapy] THEN imputed start date = 31DECYYYY;

    ELSE IF YYYY = Year of min [max(PD date + 1, last dose of study treatment + 1), end date of new anticancer therapy]

    THEN imputed start date = min [max(PD date + 1, last dose of study treatment + 1), end date of new anticancer therapy]

    ELSE IF YYYY > Year of min [max(PD date + 1, last dose of study treatment + 1), end date of new anticancer therapy]

    THEN imputed start date = 01JANYYYY
  - Both Year (YYYY) and Month (MMM) for start of anticancer therapy are available

    IF

    YYYY = Year of min [max(PD date + 1, last dose of study treatment + 1), end date of new anticancer therapy], AND

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

    THEN

    imputed start date = DAY (Last day of MMM) MMM YYYY ;

    ELSE IF

    YYYY = Year of min [max(PD date + 1, last dose of study treatment + 1), end date of new anticancer therapy], AND

    MMM = Month of min [max(PD date + 1 day, last dose of study treatment + 1 day), end date of new anticancer therapy]

    THEN

    imputed start date = min [max(PD date + 1 day, last dose of study treatment + 1 day), end date of new anticancer therapy]);

    ELSE IF

    YYYY = Year of min [max(PD date + 1, last dose of study treatment + 1), end date of new anticancer therapy], AND

MMM > Month of min [max(PD date + 1 day, last dose of study treatment + 1 day), end date of new anticancer therapy]

THEN

imputed start date = 01 MMM YYYY;

ELSE IF

YYYY < Year of min [max(PD date + 1, last dose of study treatment + 1), end date of new anticancer therapy]

THEN

imputed start date = DAY (Last day of MMM) MMM YYYY;

ELSE IF

YYYY > Year of min [max(PD date + 1, last dose of study treatment + 1), end date of new anticancer therapy]

THEN

imputed start date = 01 MMM YYYY.

#### 5.3.2.5. Other Dates

Imputation methods for other partial dates 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.

### 5.3.3. 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. Adverse Events

#### 6.1.1.1. Main Analysis

**Analysis set**: Safety: All enrolled participants who take at least 1 dose of Lorlatinib
**Analysis methodology**:

- AE incidence rate is the number of patients with any AE occurring at least once in the study population .
- All Adverse Events (AEs) will be coded using the MedDRA.
- All analyses will be based on treatment emergent events unless otherwise specified. Treatment emergent is defined in Section 3.5.1.

**Intercurrent events and missing data**:

- All data after the intercurrent event "start of subsequent anticancer therapy (-1 day)" or "35 days after treatment discontinuation" will be excluded from summaries but will be listed regardless of dosing interruptions or dosing compliance.

**Summaries used for reporting:**

- 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 associated with dose interruptions;
    - AEs associated with dose reductions;
    - AEs associated with withdrawal;

  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 (SOC) 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, 3-4 and 5 Events (All Causality) by Preferred Term and Maximum Toxicity Grade;
  - Treatment Emergent Adverse Events Associated with Dose Interruptions (All Causality);
  - Treatment Emergent Adverse Events Associated with Dose Reductions (All Causality);
  - Treatment Emergent Adverse Events Associated with Withdrawal (All Causality);
  - Treatment Emergent Adverse Events Associated with Dose Interruptions (Treatment Related);
  - Treatment Emergent Adverse Events Associated with Dose Reductions (Treatment Related);
  - Treatment Emergent Adverse Events Associated with 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 5.3.3, 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.

- Detailed information collected for each AE will be listed with a description of the event, duration, whether the AE was serious, intensity, relationship to study treatment, action taken, and clinical outcome.

- For AEs of special interest as specified in 3.5.2, these analyses will be performed:
  - Treatment Emergent Events by Maximum Toxicity Grade (All Causality);
  - Treatment Emergent Events by Maximum Toxicity Grade (Treatment Related);

- Regarding deaths, the following analysis will be performed:
  - 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).

#### 6.1.1.2. Additional Analysis

**Basic Results**

For summaries required for basic results disclosures in the US and EU the following 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.

### 6.2. Secondary Endpoints

#### 6.2.1. Confirmed OR

**Analysis set**: Safety: All enrolled participants who take at least 1 dose of Lorlatinib
**Analysis methodology**:

- Objective Response Rate (ORR) defined as the percentage of participants 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 investigator from the date of treatment start until documented

disease progression or start of new anticancer 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 anticancer 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 anticancer
- SD (for participants with at least one measurable lesion at baseline) = at least one SD assessment (or better and not qualifying for CR or PR) ≥ 6 weeks after date of treatment start and before progression and the start of new anticancer therapy
- Non-CR/Non-PD (for participants with only non-target disease at baseline) = at least one Non-CR/Non-PD assessment (or better and not qualifying for CR ≥ 6 weeks after date of treatment start and before progression and the start of new anticancer therapy
- PD = progression ≤ 13 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.

- participants without documented CR or PR will be considered as non-responders
- 95% CI interval for ORR using the Wilson's Score method

**Intercurrent events and missing data**:

- data on response after subsequent anticancer therapy is administered will be excluded
- participants with death prior to first post-baseline assessment, inadequate baseline assessment, new anticancer 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 participants with BOR of CR, PR, SD, PD, non-CR/non-PD (applicable only to participants with non-measurable disease at baseline), and NE (not evaluable)
- ORR estimated by dividing the number of participants with OR (CR or PR) by the number of participants in the safety set
- corresponding 2-sided 95% CIs

### 6.2.2. Confirmed IC-OR

**Analysis set**: Participants with CNS metastases based on Investigator Assessment

**Analysis methodology**:

The IC-OR will be summarized similar to OR (as described above in section 6.2.1), in Safety Population with CNS metastases based on investigator assessment. Surgery or radiotherapy of extracranial lesions will not affect the determination of IC-OR.

### 6.2.3. DoR

**Analysis set**: Subset of Participants with confirmed objective response

**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

DoR data will be censored as follows:

- For participants who start a new anticancer 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 anticancer therapy. Note: if date of progression occurs on the same date as the start of new anticancer 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 12 weeks until disease progression regardless of initiation of subsequent anticancer 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 24 weeks plus 2 weeks.
- 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 investigator 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 DoR analysis are presented in Table 2.

**Table 2. Outcome and event dates for DoR analyses**

| Scenario | Date of event/censoring | Outcome |
|---|---|---|
| Progression or death ≤ 26 weeks after last adequate tumor assessment | Date of progression or death | Event |
| Progression or death > 26 weeks after the last adequate tumor assessment | Date of last adequate assessment documenting no PD prior to anticancer therapy or missed assessments | Censored |
| No progression | | |
| New anticancer therapy given prior to PD | | |

**Intercurrent events and missing data**: data on response after subsequent anticancer 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 DoR 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.

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 DoR analyses**

| Hierarchy | Condition | Censoring Reason |
|---|---|---|
| 1 | Event more than 26 weeks from last adequate post-baseline tumor assessment/start date | Event after missing assessments [a] |
| 2 | No event and [withdrawal of consent date ≥ start date OR End of study (EOS) = Subject refused further follow-up] | Withdrawal of consent |
| 3 | No event and lost to follow-up in any disposition page | Lost to follow-up |
| 4 | No event and none of the conditions in the prior hierarchy are met | Ongoing without an event |

[a] more than 26 weeks after last adequate tumor assessment.

### 6.2.4. IC-DoR

**Analysis set**: Subset of Safety Participants with confirmed Intracranial objective response

**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 IC-DoR will be identical to the censoring rules presented above for DoR.

**Intercurrent events and missing data**: data on response after subsequent anticancer therapy is administered will be excluded.

**Summaries used for reporting:** The IC-DoR will be summarized similar to DoR (as described above in section 6.2.3), in Participants with CNS metastases. Surgery or radiotherapy of extracranial lesions will not affect the determination of IC-DoR.

## 6.3. Other Endpoint(s)

Not applicable.

## 6.4. Subset Analyses

Not applicable.

## 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)
    - ECOG Performance status

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

- **Disease Characteristics**

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

- 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)

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 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 Anticancer Treatments**

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

- Participants with at least one type of prior anticancer treatment;
- Participants with at least one prior anticancer drug therapy;
- Participants with at least one prior anticancer radiotherapy;
- Participants with at least one prior anticancer surgery.

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

- Number of prior anticancer therapy regimens: missing / 1 / 2 / 3 / ≥4;
- Number of participants who received prior chemotherapy
- Number of participants who received 1$^{st}$ generation (Crizotinib) or 2$^{nd}$ generation (Alectinib, Certinib or Brigatinib) ALK Inhibitor (ALKi) as Prior ALKi

The prior anticancer drugs will be coded in the World Health Organization (WHO) Drug coding dictionary.

### 6.5.2. Study Conduct and Participant Disposition

#### 6.5.2.1. Disposition

A summary of the number of participants enrolled by site will be provided for the Enrolled analysis set.

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

#### 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 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 as 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.

The following define 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 Non-drug 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 3.5.1) 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 anticancer treatments described in section 6.5.5, which were only administered prior to treatment start will be listed but not summarized.

### 6.5.5. Subsequent Anticancer Therapies/Procedures

Subsequent Anticancer Therapies and Procedures are defined as therapies entered on the short term follow up in the following:

- 'Concomitant Medications' CRF page with 'Category of Medication' = 'Follow-up Cancer Therapy')
- 'Radiation Treatment' CRF page with 'Subcategory' = 'Curative in intent'
- 'Non-drug Treatments' (with 'Category' = 'On-study Cancer Surgery' and 'Outcome of Procedure' = 'Resected' or 'Partially Resected').

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 safety analysis set.

## 6.6. Safety Summaries and Analyses

Summaries of safety parameters will be based on the safety analysis set.

### 6.6.1. Laboratory Data

Laboratory results will be converted to International System of Units (Système International d'unités, SI) units which will be used for applying toxicity grades and for all summaries.

Quantitative data will be summarized using simple descriptive statistics (mean, Std Dev, median, quartiles, minimum, and maximum) of actual values and change from baseline for each nominal visit over time (i.e. unscheduled assessments will be excluded). The total number of participants for change from baseline will include all participants who have both a baseline and a value at the nominal visit.

As described in Section 3.4, baseline will be defined as the last assessment performed on or prior to date of the first dose of study treatment. If there are multiple assessments that meet the baseline definition on the same day without the ability to determine which was truly last, then the worst grade will be assigned as the baseline grade. Several of the CTCAE terms (including Hypo/Hypercalcemia, Chronic Kidney Disease, and Activated Partial Thromboplastin) can be derived using several laboratory tests (analytes).

Results collected as strict inequalities (e.g., >10, <10) will be converted to numeric values subtracting a factor of <0.001>. Expressions of the form" ≥" or "≤" will be converted to the end point. These numeric values will be evaluated for clinically significant abnormalities but will not be included in calculations of summary statistics.

Additionally, laboratory results will be programmatically classified according to NCI-CTCAE version 4.03 grade. Non-numerical qualifiers will not be taken into consideration in the derivation of grade (e.g. hypokalemia Grade 1 and Grade 2 are only distinguished by a non-numerical qualifier and therefore Grade 2 will not be derived). In summary statistics the number and percentage of participants corresponding to grades that only include non-quantitative criteria will be displayed as a blank or NA (not assessed) rather than 0. If there is any overlap between grade criteria (e.g. CTCAE grading criteria for Creatinine Increased – a value can fall into one range based on comparison to Upper Limit of Normal (ULN) and another range based on comparison to baseline), the highest (worst) grade would be assigned to that record. Grade 5 is defined in the CTCAE criteria guidance as an event with an outcome of death. Since laboratory data does not collect an outcome, Grade 5 is not used when programmatically grading laboratory data.

Grade 0 or Outside Toxicity Reference (OTR) is not defined specifically by in the CTCAE guidance. However, programmatically this is used as a category to represent those participants who did not meet any of the Grades 1 to 4 criteria. If the laboratory value is evaluable for CTCAE criteria grading (numeric value is present, valid units and ranges are present as required to allow conversion to standard units and grading), and does not qualify for any of the Grade 1-4 criteria for a given lab test, then the value is assigned as Grade 0 or OTR.

Several of the CTCAE terms (including Hypo/Hypercalcemia, Chronic Kidney Disease, and Activated Partial Thromboplastin) can be derived using several laboratory tests (analytes).

Abnormalities will be described using the worst grade by scheduled timepoint and overall. Worst case overall will be determined from scheduled and unscheduled visits. Several laboratory tests have bi-directional grading criteria defined so that both low (hypo) and high (hyper) values can be graded separately. Each criterion will be summarized separately. In the cases where a value is graded as a Grade 1, 2, 3, or 4 for one of the directions, that value will also be assigned as a Grade 0 for the opposite direction for that test. For example, a value meeting the criteria for Grade 3 Hypercalcemia will be classified as a Grade 0 Hypocalcemia. For CTCAE terms that can be derived using one of several laboratory tests, the maximum post-baseline grade for a given participant and CTCAE term will be the maximum across all possible laboratory tests.

Additional laboratory results that are not part of NCI-CTCAE will be presented according to the following categories by scheduled timepoint as well as overall: below normal limit, within normal limits, and above normal limits. In the unlikely event that for a given participant, clinically significant abnormalities are noted in both directions (e.g., > ULN and < Lower Limit of Normal (LLN)), then both abnormalities are counted.

**Liver function tests**: Alanine aminotransferase (ALT), aspartate aminotransferase (AST), Alkaline Phosphatase (ALP), and total bilirubin (TBILI) are used to assess possible drug induced liver toxicity. The ratios of test result over the ULN will be calculated and classified for these three parameters during the on-treatment period.

Summary of liver function tests will include the following categories. The number and percentage of participants with each of the following during the on-treatment period will be summarized:

- ALT ≥ 3×ULN, ALT ≥ 5xULN, ALT ≥ 10×ULN, ALT ≥ 20×ULN
- AST ≥ 3×ULN, AST ≥ 5xULN, AST ≥ 10×ULN, AST ≥ 20×ULN
- (ALT or AST) ≥ 3×ULN, (ALT or AST) ≥ 5×ULN, (ALT or AST) ≥ 10×ULN, (ALT or AST) ≥ 20×ULN
- TBILI ≥ 2×ULN
- Concurrent ALT ≥ 3×ULN and TBILI ≥ 2×ULN
- Concurrent AST ≥ 3×ULN and TBILI ≥ 2×ULN
- Concurrent (ALT or AST) ≥ 3×ULN and TBILI ≥ 2×ULN
- Concurrent (ALT or AST) ≥ 3×ULN and TBILI ≥ 2×ULN and ALP > 2×ULN
- Concurrent (ALT or AST) ≥ 3×ULN and TBILI ≥ 2×ULN and ALP ≤ 2×ULN or missing

Concurrent measurements are those occurring on the same date.

Categories will be cumulative, i.e., a participant with an elevation of AST ≥10×ULN will also appear in the categories ≥5×ULN and ≥3×ULN. Liver function elevation and possible Hy's Law cases will be summarized using frequency counts and percentages.

An evaluation of Drug-Induced Serious Hepatotoxicity (eDISH) plot will also be created, with different symbols for different treatment arms, by graphically displaying

- peak serum ALT(/ULN) vs peak total bilirubin (/ULN) including reference lines at ALT=3×ULN and total bilirubin=2×ULN.
- peak serum AST(/ULN) vs peak total bilirubin (/ULN) including reference lines at AST=3×ULN and total bilirubin=2×ULN.

In addition, a listing of all TBILI, ALT, AST and ALP values for participants with a post-baseline TBILI ≥ 2×ULN, ALT≥ 3×ULN or AST ≥ 3×ULN will be provided.

### 6.6.2. Vital Signs

Vital signs data includes weight, pulse, systolic blood pressure, and diastolic blood pressure. Vital sign summaries will include all vital sign assessments from the on-treatment period. All vital sign assessments will be listed, and those collected outside the on-treatment period will be flagged in the listing. Measurements were only to be provided once per timepoint. If multiple assessments are provided per timepoint, the maximum value will be used for reporting.

Vital signs data will be summarized using simple descriptive statistics (mean, Std Dev, median, quartiles, minimum, and maximum) of actual values and change from baseline for each nominal visit over time (i.e. unscheduled assessments will be excluded). The total number of participants for change from baseline will include all participants who have both a baseline value and a value at the nominal visit. Baseline will be selected as defined in Section 3.4 .

The number and percent of participants in each of the following minimum and maximum blood pressure, body weight, and pulse categories will be presented:

- Increase in Systolic Blood Pressure ≥40 mmHg
- Decrease in Systolic Blood Pressure ≥ 40 mmHg
- Increase in Diastolic Blood Pressure ≥20 mmHg
- Decrease in Diastolic Blood Pressure ≥20 mmHg
- Increase in Diastolic Blood Pressure ≥60 mmHg
- Maximum Pulse Rate > 120 bpm
- Minimum Pulse Rate < 50 bpm
- Maximum increase in pulse rate ≥ 30 bpm
- Maximum decrease in pulse rate ≥ 30 bpm
- Decrease in Body Weight ≥ 10%
- Increase in Body Weight between 10% and 20%
- Increase in Body Weight ≥ 20%

All assessments, including unscheduled assessments will be considered. A participant can be included in multiple categories if different criteria are met at different timepoints.

### 6.6.3. Electrocardiograms

ECG summaries will include all ECG assessments from the on-treatment period. All ECG assessments will be listed, and those collected outside the on-treatment period will be flagged in the listing.

The analysis of QT data is complicated by the fact that the QT interval is highly correlated with heart rate. Because of this correlation, formulas are routinely used to obtain a corrected value, denoted by QTc, which is independent of heart rate. This QTc interval is intended to represent the QT interval at a standardized heart rate.

Fridericia's correction (QTcF) will be programmatically derived using the following formula:

$$QTcF(m\sec) = QT(m\sec) / \sqrt[1/3]{RR(\sec)}$$

and Bazett's correction (QTcB) will be programmatically derived using the following formula:

$$QTcB(m\sec) = \frac{QT(m\sec)}{\sqrt{RR}(\sec)},$$

where RR represents the RR interval of the ECG, in seconds.

The correlation between RR and QTcF will be explored graphically. If these are correlated and there are a sufficient number of participants (e.g. >30) with baseline ECGs, a study specific correction (QTcS) will be performed as follows:

- b will be estimated from ln(QT)=a+b*ln(RR)
- and QTcS will be derived as QTcS=QT(msec)\(RR(sec))^1\b

Data will be summarized using QTcB and QTcF. However, if these are not appropriate for the data set due to an observed large correlation between corrected QT and HR using the baseline assessments, the results will also be summarized using QTcS.

QT, heart rate, QTcB and QTcF will be summarized using simple descriptive statistics (mean, Std Dev, median, quartiles, minimum, and maximum) of actual values and change from baseline for each nominal visit over time (i.e. unscheduled assessments will be excluded). The total number of participants for change from baseline will include all participants who have both a baseline and a value at the nominal visit. Baseline will be selected as defined in Section 3.4 .

The mean absolute QTc, QTcB, QTcF, RR, PR, and QRS will be presented with two-sided 95% confidence intervals and the baseline adjusted mean QTc, QTcB, QTcF, RR, PR, and QRS will be presented with two-sided 90% confidence intervals.

Additionally, QTcB and QTcF (and QTcS if applicable) will be summarized by maximum on-treatment values using the following categories

- ≤ 450 msec
- > 450 msec but ≤ 480 msec;
- > 480 msec but ≤ 500 msec;
- > 500 msec.

Unscheduled assessments will be utilized in addition to planned assessments.

Shift tables will be provided for baseline value versus worst on-treatment value.

Additionally maximum increases from baseline (including scheduled and unscheduled assessments) will be summarized based on the following categories*:*

- Change > 60 msec,
- Change >30 msec but ≤ 60 msec,
- Change ≤ 30 msec

For QRS maximum increases from baseline, the following categories will be applied:

- QRS change ≥50% if absolute baseline value was <100 msec,
- QRS change ≥25% if absolute baseline value was ≥100 msec

For PR interval, the number (%) of subjects with maximum post-dose PR interval values and maximum increases from baseline in the following categories will be tabulated:

| | |
|---|---|
| Absolute Value (msec) | < 160 |
| | ≥160 - < 180 |
| | ≥180 - <200 |
| | ≥200 - <220 |
| | ≥220 - <240 |
| | ≥240 – 260 |
| | ≥260 |
| Absolute Change (msec) | 40 - <60 |

| | |
|---|---|
| | ≥60 - <80 |
| | ≥80 |
| Relative Change from baseline | >25% |

### 6.6.4. Performance Status

ECOG performance status with shift from ECOG=0 or 1 to ECOG 2 or higher will also be presented in a data listing.

### 6.6.5. Physical Examination

Physical examination findings will only be listed.

## 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 |
| ALP | Alkaline Phosphatase |
| ALT | Alanine Aminotransferase |
| AST | Aspartate Aminotransferase |
| ATC | Anatomic Therapeutic Chemical |
| BOR | Best Overall Response |
| CI | Confidence Interval |
| CNS | Central Nervous System |
| CR | Complete Response |
| CRF | Case Report Form |
| CSR | Clinical Study Report |
| CT | Computerized Tomography |
| DI | Dose Intensity |
| DoR | Duration of Response |
| ECG | Electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| eDISH | Evaluation of Drug-Induced Serious Hepatotoxicity |
| EGFR | Epidermal Growth Factor Receptor |
| EOS | End of Study |
| EOT | End of Treatment |
| IC-CR | Intracranial Complete Response |
| IC-DoR | Intracranial Duration of Response |
| IC-OR | Intracranial Objective Response |
| IC-ORR | Intracranial Objective Response Rate |
| IC-PD | Intracranial Progressive Disease |
| IC-PR | Intracranial Partial Response |
| IOTA | Investigator Overall Tumor Assessment |
| LLN | Lower Limit of Normal |
| LPFV | Last Participant First Visit |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MRI | Magnetic Resonance Imaging |
| N/A | Not Applicable |
| ND | Not Done |
| NE | Not Evaluable |
| NR | Not Reached |
| NCI CTCAE | National Cancer Institute Common Terminology Criteria for Adverse Events |
| NSCLC | Non-Small Cell Lung Cancer |
| OR | Objective Response |
| ORR | Objective Response Rate |

| Abbreviation | Term |
|---|---|
| OTR | Outside Toxicity Reference |
| PD | Progressive Disease |
| PR | Partial Response |
| PT | Preferred Term |
| Q1 | First Quartile |
| Q3 | Third Quartile |
| QTc | QT interval corrected for heart rate |
| QTcF | QT interval calculated using Fridericia's correction factor |
| RDI | Relative Dose Intensity |
| RECIST | Response Evaluation Criteria in Solid Tumors |
| SAP | Statistical Analysis Plan |
| SD | Stable Disease |
| SI | International System of Unit |
| SOC | System Organ Class |
| Std Dev | Standard Deviation |
| TBILI | Total Bilirubin |
| TEAE | Treatment Emergent Adverse Event |
| ULN | Upper Limit of Normal |
| WHO | World Health Organization |