Janssen Research & Development

Statistical Analysis Plan

Phase 3, Open-label, Randomized Study of Lazertinib with Subcutaneous Amivantamab Administered via Manual Injection Compared with Intravenous Amivantamab in Patients with EGFR-mutated Advanced or Metastatic Non-small Cell Lung Cancer After Progression on Osimertinib and Chemotherapy

Protocol 61186372NSC3004; Phase 3

JNJ-61186372 (amivantamab) and JNJ-73841937 (lazertinib)

RYBREVANT® and LECLAZA®

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Compliance: The study described in this report was performed according to the principles of Good Clinical Practice (GCP).

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VERSION HISTORY

SAP Version History Summary

SAP Version	Approval Date	Change	Rationale
1		Not Applicable	Initial draft
2	10 November 2022	Removal of text relating to Part 2 of the study.	Part 2 of the study has been deleted. The study now only has one part, therefore headings and text identifying parts is not required.

1. INTRODUCTION

This document presents the Statistical Analysis Plan (SAP) for protocol 61186372NSC3004, a phase 3, open label, randomized study of Lazertinib with Subcutaneous Amivantamab compared with Intravenous Amivantamab in patients with EGFR-mutated Advanced or Metastatic Non-small Cell Lung Cancer After Progression on Osimertinib and Chemotherapy. The SAP contains definitions of analyses sets, derived variables, and statistical methods for all planned analyses for this study.

This SAP follows guidelines provided in the International Conference on Harmonization (ICH) Topic E9 Statistical Principles for Clinical Trials and is to be interpreted in conjunction with the clinical protocol. In the event of future amendments to the protocol, this SAP may be modified as necessary to account for changes relevant to the statistical analyses.

1.1. Trial Objectives

Primary Objective

The primary objectives are to assess the pharmacokinetic noninferiority of amivantamab SC-CF via manual injection versus amivantamab IV.

Key Secondary Objective

The key secondary objectives are to assess efficacy (objective response rate [ORR] and progression-free survival [PFS]) and safety of the different administrations.

Other Secondary Objectives

The other secondary objectives are:

- To assess amivantamab pharmacokinetics and immunogenicity to amivantamab or rHuPH20 in participants treated with amivantamab SC-CF administered via manual injection (Arm A) versus amivantamab IV (Arm B)

- To assess cancer therapy satisfaction in participants treated with amivantamab SC-CF administered via manual injection (Arm A) versus amivantamab IV (Arm B) using the modified TASQ

- Time and motion analysis in participants treated with amivantamab SC-CF administered via manual injection (Arm A) versus amivantamab IV (Arm B) based on the following:
    - Participant chair time
    - Participant time in treatment room
    - Duration of treatment administration
    - Active HCP time for drug preparation, treatment administration, and post-treatment monitoring.

Exploratory Objectives

The exploratory objectives are:

- To explore additional measures of efficacy of amivantamab SC-CF administered via manual injection (Arm A) versus amivantamab IV (Arm B).

- To explore potential mechanisms of resistance to amivantamab and lazertinib.
- To further explore cancer therapy satisfaction in participants treated with amivantamab SC-CF administered via manual injection (Arm A) versus amivantamab IV (Arm B) using PGIS and PGIC.
- To explore the relationship between PK or immunogenicity and selected endpoints (including but not limited to efficacy, safety, and/or patient-reported outcomes)

1.2. Study Design

Study 61186372NSC3004 (PALOMA-3) is a randomized, open-label, parallel, multicenter, Phase 3 study, which will optimize the administration of amivantamab in participants with EGFR mutated locally advanced or metastatic NSCLC who have progressed on or after treatment with osimertinib and platinum-based chemotherapy. The study will compare the PK, efficacy, and safety of combining lazertinib with amivantamab SC-CF administered via manual injection (Arm A) versus amivantamab IV (Arm B).

Approximately 400 participants will be enrolled in this study. Participants will be stratified by brain metastases at baseline (yes versus no), EGFR mutation (L858R versus Exon 19del), race (Asian versus Non-Asian), and last therapy (osimertinib [or another approved 3rd generation EGFR TKI] versus chemotherapy).

The study will include Screening (up to 28 days), a Treatment Phase (from randomization until the End of Treatment Visit), and a Follow-up Phase (from End of Treatment Visit until the end of study, death, lost to follow-up, or withdrawal of consent, whichever comes first).

A target of 400 participants will be randomized 1:1 between Arms A and B. An IDMC will be commissioned for this study.

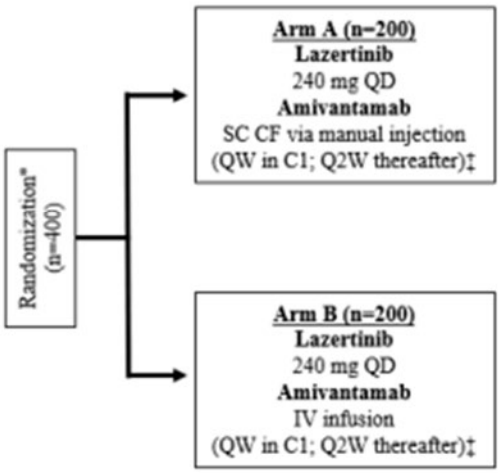
All participants will receive lazertinib 240 mg orally once daily. In cycle 1, amivantamab SC-CF by manual injection or OBDS will be administered at doses 1,600 mg (2,240 mg if body weight (BW) ≥80 kg) on days 1, 8, 15, and 22. Amivantamab IV infusion doses at 1,050 mg (1,400 mg if BW ≥80 kg) will occur on Days 1-2 (split dose), 8, 15, and 22 during cycle 1. Starting cycle 2, doses will occur on Day 1 and 15 of each 28-day cycle, amivantamab SC-CF by manual injection or OBDS at 1,600 mg (2,240 mg if BW ≥80 kg), or amivantamab by IV infusion at 1,050 mg (1,400 mg if BW ≥80 kg).

All participants will undergo regular disease assessments to monitor their underlying disease at screening, 6 (+1) weeks from randomization, every 6 (±1) weeks for the first 18 months, then every 12 (±1) weeks thereafter until progressive disease (PD).

A diagram of the study design is provided in Figure 1.

Note: For clarity this SAP uses arm names ‘A’ and ‘B’ to align with Global Protocol Amendment 2, however in other documents and systems these may be referred to as ‘A1’ and ‘B1’ as these were already in place at the time of this Amendment to remove Part 2 of the study.

Figure 1: Schematic Overview of the Study



1.3. Randomization and Blinding

Randomization will be used to minimize bias in the assignment of participants to treatment groups, to increase the likelihood that known and unknown participant attributes (e.g., demographic and baseline characteristics) are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups. Due to differences in safety profile, safety monitoring, premedication requirements, and administration, blinded study treatment and a placebo control will not be used.

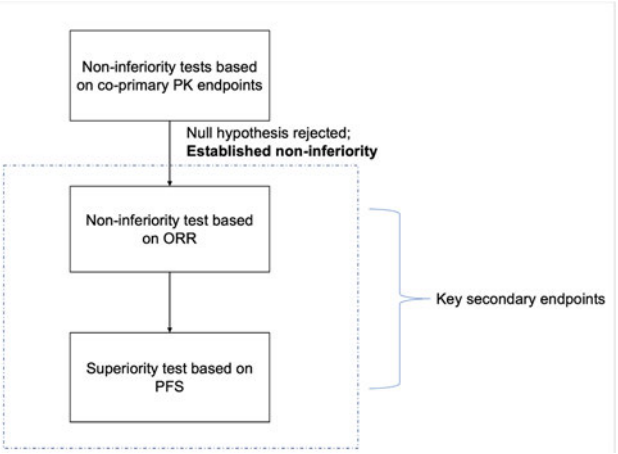
2. STATISTICAL HYPOTHESES

The primary statistical hypothesis of this study is that amivantamab SC-CF, administered via manual injection at the RP2D, is noninferior to amivantamab IV based on the co-primary pharmacokinetics endpoints, C_{trough} (at steady state [Cycle 4 Day 1] for all regions other than EU and pre-dose levels on cycle 2 Day 1 for EU only) and $AUC_{D1\text{-}D15}$ in Cycle 2. The hypotheses are the lower bounds of the 90% CI for the ratio of the geometric means of amivantamab SC-CF vs amivantamab IV are at least 80% (non-inferiority margin of 20%) for both C_{trough} (at steady state of amivantamab on Cycle 4 Day 1 for all regions other than EU and pre-dose on Cycle 2 Day 1 for EU only) and $AUC_{D1\text{-}D15}$ in Cycle 2.

A key secondary hypothesis is that amivantamab SC-CF, administered via manual injection at the RP2D, is noninferior to amivantamab IV based on ORR in the aforementioned population. The hypothesis is that the lower bounds of the 95% CI for the relative risk of amivantamab SC-CF vs amivantamab IV for ORR is 60%. Another key secondary hypothesis is that amivantamab SC-CF will reduce the risk of either disease progression or death compared with amivantamab IV.

To control familywise Type I error rate at a two-sided significance level of 0.05, a hierarchical procedure for hypothesis testing between primary PK endpoints and key secondary efficacy endpoints will be implemented. Once the null hypothesis of inferiority is rejected for both the C_{trough} at steady state and $AUC_{D1\text{-}D15}$ in Cycle 2, a testing for ORR and PFS at a two-sided significance level of 0.05 will be tested in a sequential order (Figure 2).

Figure 2: Primary and Key Secondary Endpoints Testing Strategy



2.1. Non-inferiority Margins Justification

For the co-primary pharmacokinetic endpoints, C_{trough} (at steady state on Cycle 4 Day 1 for all regions other than EU and pre-dose on Cycle 2 day 1 for EU only) and $AUC_{D1\text{-}D15}$ in cycle 2, the non-inferiority of amivantamab SC-CF relative to amivantamab IV is defined using a non-inferiority margin of at least 80% of the ratio of geometric mean of C_{trough} (at steady state on Cycle 4 Day 1 for all regions other than EU and pre-dose on Cycle 2 day 1 for EU only) and $AUC_{D1\text{-}D15}$ in cycle 2. Since these are PK endpoints, the selection of non-inferiority margin and the choice of alpha level follow the convention for bioequivalence studies.

The key secondary hypothesis defines the clinical non-inferiority of Amivantamab SC-CF relative to Amivantamab IV using a 60% retention of the lower bound (23.3%) of the 95% CI of ORR from previous clinical study 73841937NSC1001. In a previous clinical study (73841937NSC1001), of 50 participants with locally advanced or metastatic NSCLC with EGFR Exon 19del or Exon 21 L858R mutations whose disease had progressed on or after treatment with osimertinib and platinum-based chemotherapy and who were treated with the combination of amivantamab IV and lazertinib, an ORR of 32.1% (95% CI:23.3%, 41.8%) was observed. The 60% retention will result in minimal loss of benefit in terms of observed ORR. The clinical relevance of the 60% retention of ORR was justified based on the benefit/risk of amivantamab SC of similar efficacy from early efficacy and pharmacokinetics data.

3. SAMPLE SIZE DETERMINATION

200 participants will be randomized to Arm A, and 200 participants will be randomized to Arm B (Figure 1).

The study is designed to establish noninferiority based on the co-primary pharmacokinetics endpoints, C_{trough} (at steady state of amivantamab on Cycle 4 Day 1 for all regions other than EU and pre-dose on Cycle 2 Day 1 in EU only) and $AUC_{D1\text{-}D15}$ in Cycle 2, between amivantamab SC-CF and amivantamab IV. Amivantamab SC-CF will be considered noninferior to IV if the lower bound of the 90% CI for the ratio of the geometric means of C_{trough} (at steady state of amivantamab on Cycle 4 Day 1 for all regions other than EU and pre-dose on Cycle 2 Day 1 in EU only) and AUC_{D1D15} in Cycle 2 is at least 80% (noninferiority

margin of 20%). The planned 400 participants (200 from Arm A and 200 from Arm B) will provide a power >95% for a one-sided alpha of 0.05 for each of the endpoints. This assumes true geometric mean ratios of C_{trough} and $AUC_{D1\text{-}D15}$ to be 1 between the 2 treatment groups, and a coefficient of variation (CV) of 56% for both endpoints.

One of the key secondary objectives is to assess efficacy of SC-CF (Arm A) compared to IV (Arm B) in terms of ORR. In a previous clinical study (73841937NSC1001), of 50 participants with locally advanced or metastatic NSCLC with EGFR Exon 19del or Exon 21 L858R mutations whose disease had progressed on or after treatment with osimertinib and platinum-based chemotherapy and who were treated with the combination of amivantamab IV and lazertinib, an ORR of 32.1% (95% CI:23.3%, 41.8%) was observed. Non-inferiority of amivantamab SC-CF to amivantamab IV in the current study is defined using a 60% retention of the lower bound (23.3%) of the 95% CI from Study 73841937NSC1001. With a planned 1:1 randomization, the sample size of 400 participants will provide 80% power to demonstrate the non-inferiority of Arm A compared with Arm B, with a one-sided alpha of 0.025, assuming the true ORR is the same for both treatment arms.

4. POPULATIONS (ANALYSIS SETS) FOR ANALYSIS

For purposes of analysis, the following populations are defined:

Analysis Sets	Description
Full Analysis Set (FAS)	The full analysis set (FAS) includes all participants who were randomized in the study.
PK Primary Endpoint Evaluable	All randomized participants who receive all doses in Cycle 1-3, without dose modifications and provide all necessary PK samples to derive primary PK endpoints C_{trough} (on Cycle 4 Day 1 for all regions other than EU and pre-dose on Cycle 2 Day 1 for EU only), and all randomized participants who receive all doses up to Cycle 2 Day 1, without dose modifications and provide all necessary PK samples to derive primary PK endpoint $AUC_{D1\text{-}D15}$ in Cycle 2.
Other PK Evaluable	All randomized participants who receive at least 1 dose of study treatment and have at least 1 evaluable postbaseline concentration measurement. Participants will be excluded from the PK analysis if their data do not allow for accurate assessment of the PK.
Safety	All randomized participants who receive at least 1 dose of study drug.
Immunogenicity Analysis Set	All participants who receive at least 1 dose of study drug and provide at least 1 post dose immunogenicity sample.
Biomarker	All participants who receive at least 1 dose of study drug and provide at least 1 post dose biomarker sample.

5. STATISTICAL ANALYSES

5.1. General Considerations

Continuous variables will be summarized using number of participants (n), mean, standard deviation (SD), median, minimum, and maximum. Discrete variables will be summarized with frequency counts and percentages. The Kaplan-Meier product limit method and a stratified Cox model will be used to estimate

time-to-event variables and to obtain the HR and confidence interval. Unless otherwise specified, stratified log-rank tests will be used to test the treatment effect for time-to-event variables; response rate variables will be evaluated using the chi square statistic or the exact test if the cell counts are small.

5.1.1. Visit Windows

For analyses of data by cycle, if data are collected by date, the corresponding study evaluations will be assigned to actual sequential cycles, which are derived from the study drug administration data. The start date of a cycle is defined as the first scheduled dose date of the study drug for that particular cycle, and the end date of a cycle is the start date of the next cycle minus 1. For the last cycle, the end date is defined as the end of treatment visit date or the minimum of last dose plus 30 days or subsequent anticancer therapy minus 1 day if the end of treatment visit date is not available.

In general, if data (e.g., laboratory and vital sign etc.) are collected by cycle, the nominal cycle will be used to summarize the data.

5.1.2. Study Day

Study day is defined as:

- Study day = date of assessment – first dosing date +1 for any assessment on or after the first dosing date; otherwise, study day is defined as date of assessment – first dosing date. Day 1 is the first dosing date. There is no 'Day 0'.

5.1.3. Pooling Algorithm for Analysis Centers

Data from all study centers will be pooled for analyses.

5.1.4. Study Treatment and Study Drug

For the purposes of this study, 'study treatment' refers to amivantamab SC-CF administered via manual injection in combination with lazertinib (Arm A) and amivantamab IV in combination with lazertinib (Arm B. 'Study drug' refers to an individual drug within a specific cohort, amivantamab SC-CF or amivantamab IV and lazertinib.

5.1.5. Study Drug Dosing Date

Study drug dosing date is the date on which a subject actually received a study drug (a partial or complete dose). For participants who received the study drug, the first study drug date is defined as the earliest date of non-zero dose of the study drug. The last study drug date is defined as the latest date of non-zero dose of the study drug.

5.1.6. Baseline Measurement

Baseline measurement is defined as the non-missing value taken closest to but prior to the first dose of study drug (including time if time is available).

5.1.7. Unique Lab Value

In general, in instances when there are multiple records at a given visit date for lab parameters, the following rules will be applied to select the unique lab value for analysis: in the case of multiple records from the local lab, select the most recent lab value as the unique non-missing lab value.

5.1.8. Relative Dose Intensity

The relative dose intensity (%) defined as the ratio of total received dose versus total prescribed dose, will be summarized by descriptive statistics.

5.2. Participant Dispositions

Screened participants and reason for screen failures will be summarized overall.

The number of participants in the following disposition categories will be summarized throughout the study by intervention group and overall:

- Participants randomized
- Participants who received study intervention
- Participants who completed the study
- Participants still on the study
- Participants who discontinued study intervention (any of the study drugs)
- Reasons for discontinuation of study intervention (as indicated by the investigators)
- Participants who terminated study prematurely
- Reasons for termination of study (as indicated by the investigators)

Listings of participants will be provided for the following categories:

- Participants who discontinued study intervention
- Participants who terminated study prematurely
- Participants who were unblinded during the study period
- Participants who were randomized yet did not receive study intervention.

5.3. Primary Endpoint(s) Analysis

5.3.1. Definition of Endpoint(s)

The co-primary PK noninferiority endpoints of are defined as follows:

- C_{trough} on Cycle 4 Day 1 (for all regions other than EU)
- C_{trough} prior to first dose at Cycle 2 Day 1 (EU only)
- $AUC_{D1\text{-}D15}$ in Cycle 2 (for all regions)

5.3.2. Estimand (non-EU)

The primary estimand for the co-primary PK endpoints for all regions except EU is defined by the following components:

Study treatment:

Experimental: Amivantamab SC-CF administered via manual injection

Control: Amivantamab IV

Population: participants with EGFR-mutated locally advanced or metastatic NSCLC who have progressed on or after treatment with osimertinib and platinum-based chemotherapy.

Variable: PK endpoints, C_{trough} at steady state (Cycle 4 Day 1]) and AUCD1-D15 in Cycle 2.

Population-level summary: Ratio of geometric means of C_{trough} at steady state (Cycle 4 Day 1) and $AUC_{D1\text{-}D15}$ in Cycle 2 between SC-CF and IV administrations.

Intercurrent events and their corresponding strategies: no additional intercurrent events

5.3.3. Estimand (EU)

The primary estimand for the co-primary PK endpoints for all EU regions (as requested by the agency, EMEA) is defined by the following components:

Study treatment:

Experimental: Amivantamab SC-CF administered via manual injection

Control: Amivantamab IV

Population: participants with EGFR-mutated locally advanced or metastatic NSCLC who have progressed on or after treatment with osimertinib and platinum-based chemotherapy.

Variable: PK endpoints, C_{trough} prior to first dose at Cycle 2 Day 1 and $AUC_{D1\text{-}D15}$ in Cycle 2.

Population-level summary: Ratio of geometric means of C_{trough} prior to first dose at Cycle 2 Day 1 and $AUC_{D1\text{-}D15}$ in Cycle 2 between SC-CF and IV administrations.

Intercurrent events and their corresponding strategies: no additional intercurrent events

5.3.4. Analysis Methods

The ratio of the geometric means and the corresponding 90% CI between Arm A and Arm B for each primary endpoint will be provided based on the PK Analysis Set. The primary hypothesis tests will be based on one-sided test at significance level of alpha = 0.05 to demonstrate the non-inferiority of the amivantamab SC-CF relative to amivantamab IV. If the non-inferiority of the

amivantamab SC-CG relative to amivantamab IV is claimed and the lower bounds of the 90% CI for the ratio of the geometric means of amivantamab SC-CF vs amivantamab IV are at least 80% (non-inferiority margin of 20%) for both C_{trough} (at steady state of amivantamab in Cycle 4 for all regions other than EU and prior to first dose at Cycle 2 Day 1 for EU only) and AUC_{D1-D15} in Cycle 2, then non-inferiority based on key secondary end points will be tested.

To control familywise Type I error rate at a two-sided significance level of 0.05, a hierarchical procedure for hypothesis testing between primary PK endpoints and key secondary efficacy endpoints will be implemented. Once the null hypothesis of inferiority is rejected for both the co-primary PK endpoints, ORR and PFS will be tested at a two-sided significance level of 0.05 in a sequential order.

Summary statistics such as the geometric mean, coefficient of variation, median, and range will be provided by treatment group.

5.4. Secondary Endpoint(s) Analysis

5.4.1. Key Confirmatory Secondary Endpoint(s)

Key secondary analyses will be performed at the time of the primary analysis.

5.4.1.1. Objective Response Rate (ORR)

5.4.1.1.1. Definition

ORR is defined as the proportion of participants who achieve either a complete response or partial response, as defined by RECIST v1.1. Data obtained up until progression or last evaluable disease assessment in the absence of progression will be included in the assessment of ORR. However, any complete response or partial response, which occurred after a further anticancer therapy was received, will not be included in the numerator for the ORR calculation.

5.4.1.1.1.1. Estimand

Study Treatment

Experimental: amivantamab SC-CF administered via manual injection

Control: amivantamab IV

Population: Participants with EGFR mutation (Exon 19del or Exon 21 L858R substitution) positive, locally advanced or metastatic NSCLC who have progressed on or after treatment with osimertinib and platinum-based chemotherapy.

Variable: ORR

Summary Measure (Population-level summary): odds ratio of amivantamab SC-CF vs amivantamab IV

Intercurrent events and their corresponding strategies:

Intercurrent Events	Name of Strategy for Addressing Intercurrent Events and Its Description
Study treatment switching to other anticancer therapy	**Hypothetical strategy**: use best overall response until subsequent anti-cancer therapy

5.4.1.1.1.2. Analysis Methods

ORR will be analyzed based on the Full Analysis Set.

ORR will be analyzed using a logistic regression stratified by randomization strata. The results of the analysis will be presented in terms of a risk ratio together with its associated 95% confidence intervals. If the lower bound of the 95% CI is ≥60%, the non-inferiority of amivantamab SC-CF relative to amivantamab IV will be concluded. If non-inferiority in ORR is established and the lower limit of the 95% CI of the relative risk is >100%, the superiority of amivantamab SC-CF relative to amivantamab IV will be concluded.

5.4.1.2. Progression-free Survival (PFS)

Progression-free Survival (PFS) is defined as the time from randomization until the date of objective disease progression or death, whichever comes first, based on RECIST v1.1. Participants who have not progressed or have not died at the time of analysis will be censored at their last evaluable RECIST v1.1 assessment date.

PFS is calculated in months as follows:

- PFS = (date of PD/death or censoring – date of randomization + 1) / (365.25/12).

Key censoring rules for PFS are summarized in Table 1 below.

Table 1. Key censoring rules for PFS

Situation	Censoring Rule
No evaluable baseline or postbaseline disease assessment	Censored at the date of randomization
Lost to follow-up or withdraw from study	Censored at the date of last evaluable disease assessment
No documented disease progression or death	Censored at the date of last evaluable disease assessment
Documented disease progression or death after 2 or more consecutive missed/unevaluable disease assessments*	Censored at the date of last evaluable disease assessment before the missed/unevaluable visits

*If no evaluable disease assessment before the consecutive missed/unevaluable visits, participants will be censored at the date of randomization.

5.4.1.2.1. Estimand

The primary estimand for PFS, the main clinical quantity of interest to be estimated, is defined by the following components:

Study treatment:

Experimental: Amivantamab SC-CF administered via manual injection

Control: Amivantamab IV

Population: participants with EGFR-mutated locally advanced or metastatic NSCLC who have progressed on or after treatment with osimertinib and platinum-based chemotherapy

Variable: time to event, PFS

Population-level summary: odds ratio for amivantamab SC-CF vs amivantamab IV

Intercurrent events and their corresponding strategies

Intercurrent Events	Name of Strategy for Addressing Intercurrent Events and Its Description
Study treatment discontinuation due to any reason	**Treatment Policy strategy:** use time to disease progression or death, regardless of whether or not study treatment discontinuation had occurred
Study treatment switching to other anticancer therapy	**Treatment Policy strategy:** use time to disease progression or death, regardless of whether or not started subsequent anticancer therapies
Death	**Composite Variable strategy:** death being a component of the variable

5.4.1.2.2. Analysis Methods

The median PFS and 95% CI in each treatment group will be estimated using the Kaplan-Meier method. The PFS distributions between the 2 treatment groups will be compared using the stratified log-rank test. The treatment effect (hazard ratio) and its 2-sided 95% CI will be estimated using a stratified Cox regression model with treatment as the sole explanatory variable.

5.4.2. Supportive Secondary Endpoint(s)

5.4.2.1. Definition of Endpoint(s) and Analysis Methods

Duration of Response (DoR)

DoR is defined as the time from the date of first documented response (CR or PR) until the date of documented progression or death, whichever comes first. The end of response should coincide with the date of progression or death from any cause used for the PFS endpoint. If a participant does not progress following a response, then his/her duration of response will use the PFS censoring time.

For DoR, a Kaplan Meier plot and median duration of response with 95% confidence interval (calculated from the Kaplan Meier estimate) will be presented by treatment group for participants who have PR or CR as their best response.

Time to Response (TTR)

Time to response (i.e., time to first response) is defined as the time from the date of randomization to the date of first documentation of a response (PR or CR) prior to any disease progression and subsequent anticancer therapy, as defined by BICR using RECIST v1.1., for participants who have PR or CR as their best response.

A descriptive summary for TTR will be provided.

Modified Therapy Administration Satisfaction Questionnaire

The modified TASQ is an 11-item questionnaire measuring the impact of each mode of treatment administration on five domains: Physical Impact, Psychological Impact, Impact on Activities of Daily Living, Convenience, and Satisfaction and used a variety of response scales, including a five-point scale, categorical scale, and a dichotomous scale. Each domain is scored on a scale of 0 to 100, with higher scores indicative of more positive feelings toward therapy. The score for each domain was averaged among all participants. Example questions include, "How satisfied or dissatisfied were you with the SC injection/IV infusion?", "How much pain did you experience at the site of the SC injection/IV site?", and "How convenient is it for you to get your SC injection/IV infusion?" The modified TASQ-IV will be completed by participants in Arm B and the modified TASQ-SC by participants in Arm A. The modified TASQ should be completed after the study drug administration.

The TASQ was derived from the Rituxan Administration Satisfaction Questionnaire (RASQ). Modification addresses the administration site of amivantamab. TASQ is designed for an adult population to measure the impact of the mode of treatment administration on 5 domains, including 9 items: Physical Impact (3 items), Psychological Impact (1 item), Impact on Activities of Daily Living (1 item), Convenience (2 items), and Satisfaction (2 items). Recall/Observation period is based on participants most recent SC injection/IV infusion (Theodore-Oklota, 2016).

Patient Global Impression of Severity (PGIS) and Patient Global Impression of Change (PGIC) are single-item questionnaires that provide an anchor-based comparison for the TASQ. The PGIC will not be administered at the first visit because it captures change.

The PGIS and PGIC should be conducted/completed before any tests, procedures, or other consultations to prevent influencing participant responses, when possible.

The modified-TASQ is a secondary endpoint, not a part of the statistical hierarchy. Non-inferiority will not be analyzed for this endpoint. Type 1 error control will not be applied to patient reported outcome data.

Analysis of PRO data will be performed on Full Analysis Set. For participants with multiple records at the same visit, the closest one to the visit date will be selected as scheduled assessment, and other will be unscheduled assessments. Compliance rates for completion of modified-TASQ

at each time point will be generated based on the actual number of assessments received over the number of expected. For modified-TASQ domain scores (physical impact, psychological impact, impact on activities of daily living, convenience, and satisfaction), and single symptom items, descriptive statistics will be reported at baseline and at each visit for absolute value and for change from baseline. Line plots of the change from baseline with standard error over time by treatment group will be displayed.

Time and motion analysis

The time and motion analysis are a healthcare burden impact study investigating differences in participant chair time, treatment room time, duration of treatment administration, and active HCP time for drug preparation, treatment administration, and post-treatment monitoring. For time and motion analysis, summary statistics will be provided by treatment groups, country/territory and pooled.

Immunogenicity

The incidence of anti-amivantamab antibodies will be summarized for all participants who receive a dose of amivantamab and have appropriate samples for detection of antibodies to amivantamab. The incidence of anti-rHuPH20 antibodies will be summarized for all participants who receive a dose of amivantamab SC-CF and have appropriate samples for detection of anti-rHuPH20 antibodies.

Model predicted AUC_{ss}

Model-predicted AUC at steady state will estimate exposures for Cycle 4 Day 1- Day 15 using Population PK approach. Population PK analysis of serum concentration-time data of amivantamab will be performed using nonlinear mixed-effects modeling (NONMEM) and may be combined with similar data from other studies, with the aim of providing estimates of AUC_{ss}. Details will be provided in a population PK and exposure-response analysis plan and results of the analysis will be presented in a separate report.

Other Pharmacokinetic Endpoints

For all regions other than EU, C_{trough} of amivantamab pre-dose on Cycle 2 Day 1 and for EU C_{trough} at steady state on Cycle 4 Day 1 will be considered as supportive secondary endpoints. The ratio of the geometric means between Arm A and Arm B and the corresponding 90% CI will be provided based on the PK Analysis Set.

5.5. Tertiary/Exploratory Endpoint(s) Analysis

Overall Survival (OS)

OS is measured from the date of randomization to the date of the participant's death. If the participant is alive or the vital status is unknown, then the participant's data will be censored at the date the participant was last known to be alive. The median OS and 95% CI in each treatment

group will be estimated using the Kaplan-Meier method. The OS distributions between the 2 treatment groups will be compared using the stratified log-rank test.

Biomarkers

Biomarkers analyses will use the Biomarkers Population. Each baseline tumor status may be evaluated by ctDNA NGS analysis, for exploratory purposes, to characterize potential mechanisms of resistance to amivantamab and lazertinib, and to evaluate the presence of mutations across treatment arms, as permitted by local regulations.

Assessment of additional genes or biomarkers (DNA, RNA, or protein) relevant to lung or other cancers and assessment of the mechanism of action or metabolism of study treatments may also be performed in blood samples collected on study to better understand mechanisms of response or resistance to study treatment. Alterations in blood characteristics may be evaluated for correlation with response to study treatment, tumor burden, and disease progression as data warrant.

5.6. Safety Analyses

All safety analyses will be based on the safety analysis set based on actual intervention received, unless otherwise specified. The safety assessments to be evaluated include AEs, deaths, clinical laboratory tests (hematology, chemistry), vital signs, electrocardiogram (ECG).

For all continuous safety variables, descriptive statistics by intervention group will include the N, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized by intervention group using frequency counts and percentages.

5.6.1. Extent of Exposure

Extent of exposure to study drug will be summarized and presented on safety analysis set. Treatment duration and the total number of treatment cycles will be summarized descriptively. The number and percentage of subjected treated within each treatment cycle will also be summarized by treatment arm, and for each study drug. Treatment duration is defined as (date of last dose of study treatment – date of first dose of study treatment) +1. Descriptive statistics for duration of each study drug for each treatment arm [N, mean, SD, median, and range (minimum, maximum)] will be summarized.

The total number of injections of amivantamab SC-CF and total number of infusions of amivantamab IV received for each participant will be summarized by descriptive statistics. Cumulative duration of amivantamab will be provided by cycle (≥1 cycle, ≥2 cycles, …). The total number of amivantamab SC-CF injections / amivantamab IV infusions and the total dose of amivantamab for each participant will be summarized by descriptive statistics.

For amivantamab IV, duration of infusion in hours is derived for each visit. It includes both interruption time and actual infusion time and is calculated as maximum infusion end time –

minimum infusion start time, divided by 60 minutes. Duration of infusion of amivantamab infusion in hours will be summarized by first infusion, second infusion, and subsequent infusion.

Total dose days of study drug, defined as the total number of days that study drug was administered to the participant (excluding days off study drug), will be summarized for lazertinib descriptively. The cumulative duration of lazertinib will also be provided by month (≥1 month, ≥2 months, …).

The incidence of amivantamab dose skip due to AE will be summarized. The number (%) of participants with a dose reduction/dose not administrated will be summarized. Reasons for dose reduction/dose not administrated will also be summarized.

The number (%) of participants with cycle delay will be summarized by cohort. The reason for the cycle delay will also be summarized.

5.6.2. Adverse Events

The verbatim terms used in the CRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Any AE occurring at or after the initial administration of study intervention through the day of last dose plus 30 days or until the start of subsequent systemic anticancer therapy, if earlier, is considered to be treatment emergent. If the event occurs on the day of the initial administration of study intervention, and either event time or time of administration are missing, then the event will be assumed to be treatment emergent. If the event date is recorded as partial or completely missing, then the event will be considered to be treatment emergent unless it is known to be prior to the first administration of study intervention based on partial onset date or resolution date. All reported treatment-emergent adverse events will be included in the analysis. For each adverse event, the number and percentage of participants who experience at least 1 occurrence of the given event will be summarized by treatment arm.

The incidence (%) of TEAEs will be summarized overall, by MedDRA system organ class (SOC) and preferred term (PT), by toxicity grade, and by relationship to study drug administration.

5.6.2.1. Overview of TEAEs

An overview of TEAEs reported through the study will be provided for each treatment group. Overall summary of TEAE will include the participants with TEAEs, serious TEAEs, TEAEs related to study treatment, TEAEs of maximum toxicity grade of 1 to 5, TEAE s leading to treatment discontinuation of any study drug, and TEAAs with fatal outcome.

5.6.2.1.1. All TEAEs

- Incidence (%) of TEAEs by SOC and PT

5.6.2.1.2. Toxicity Grade 3 or Higher TEAEs

- Incidence (%) of toxicity grade 3 or higher TEAEs by SOC and PT

5.6.2.1.3. Study Drug-Related TEAEs

- Incidence (%) of TEAEs by relationship to treatment/study drug, and by SOC and PT
- Incidence (%) of TEAEs with toxicity grade 3 or higher by relationship to treatment/study drug, and by SOC and PT
- Incidence (%) of TEAEs leading to study drug interruption/ dose reduction by relationship to treatment/study drug, and by SOC and PT
- Incidence (%) of TEAEs leading to study drug discontinuation by relationship to treatment/study drug, and by SOC and PT

5.6.2.1.4. Serious TEAEs

- Incidence (%) of serious TEAEs by SOC and PT
- Incidence (%) of serious TEAEs by toxicity grade, and by SOC and PT
- Incidence (%) of serious TEAEs by relationship to treatment/study drug, and by SOC and PT
- Listing of participants with any serious TEAEs

5.6.2.1.5. TEAEs Leading to Study Drug Interruption/Dose Reduction

The incidence (%) of TEAEs leading to study drug interruption or dose reduction will be summarized by SOC and PT, respectively. The summaries will be presented for all toxicity grades and for toxicity grade 3 or higher.

5.6.2.1.6. TEAEs Leading to Discontinuation of Study Drug

The incidence (%) of TEAEs leading to study drug discontinuation will be summarized by SOC and PT, respectively. The summaries will be presented by all toxicity grades and toxicity grade 3 or higher. The AEs leading to discontinuation of any study drug are based on AEs recorded in the AE CRF page with an action taken of drug withdrawal for any study drug.

5.6.2.1.7. Adverse Events of Special Interest

AEs of special interest are pneumonitis/ILD, rash, and IRR. The MedDRA preferred terms associated with each of these categories are identified in Appendix 6. Additional information will be collected for these events.

TEAEs of special interest will be included for analysis. Incidence (%) for the following AEs will be provided for each AE of special interest as appropriate:

- TEAEs by PT
- TEAEs by toxicity grade
- TEAEs of toxicity grade 3 or higher by PT
- Serious TEAEs by PT
- TEAEs by relationship to study drug
- Serious TEAEs by PT
- Serious TEAEs by relationship to study drug

- TEAEs leading to study drug discontinuation by PT
- TEAEs leading to study drug discontinuation by relationship to study drug
- TEAEs leading to death by PT

Additional analyses will be provided based on information collected in CRF.

Pneumonitis/ILD

For participants with pneumonitis/ILD, a frequency tabulation will be provided for:

- Symptom (fever, dry cough, productive cough, dyspnea, chest pain, other)
- Pleural effusion presents at the time of the pneumonitis/ILD (yes/no）
- The relative onset day (since day 1) of pneumonitis/ILD will be summarized by descriptive statistics (N, mean, standard deviation, median, and range). All information related to pneumonitis/ILD collected in CRF page will be presented in a listing.

Rash

The relative onset day (since day 1), the duration, and the time between onset and the preceding infusion administration will be summarized for rash by descriptive statistics (N, mean, standard deviation, median, and range) in days.

ARR

The incidence (%) of ARRs leading to administration modifications (injection interrupted and injection stopped) will be presented. The relative onset day (since day 1), and duration will be summarized for ARR by descriptive statistics (N, mean, standard deviation, median, and range) in days.

Venous Thromboembolic Events (VTE)

Patients with NSCLC are at risk of developing complications, including VTE events. For participants with VTE events, frequency tabulation for relative time to diagnosis (since day 1) will be summarized by descriptive statistics (N, mean, standard deviation, median, and range) in days.

5.6.2.1.8. Deaths

Deaths due to TEAEs
The number of participants who died due to TEAEs will be summarized by PT and relationship to study drug. The TEAEs included in this table are AEs with outcome of death or toxicity grade of 5 recorded in the AE CRF page within 30 days of the last dose or until the start of subsequent anticancer therapy (if earlier).
A listing of participants who died due to TEAE will be provided.

All Deaths
A summary of all deaths and cause of death will be tabulated. Specifically, the number of participants who died during the study will be summarized. The primary cause of death collected

on the death information CRF page will be reported. Similar summaries will be presented for participants who died within 30 days of last study drug dose.

5.6.3. Clinical Laboratory Tests

Clinical laboratory tests will be displayed for the participants included in the safety analysis set. Laboratory data will be summarized by type of laboratory test. Reference ranges and markedly abnormal results will be used in the summary of laboratory data. Descriptive statistics and graphical displays will be presented for each laboratory analyte at baseline and for observed values and changes from baseline at each scheduled time point. Frequency tabulations of the laboratory abnormalities will be made. A listing of participants with any laboratory results outside the reference ranges will be provided. A listing of participants with any markedly abnormal laboratory results will also be provided.

Parameters with predefined NCI CTCAE toxicity grades will be summarized. Change from baseline to the worst AE grade experienced by the participant during the study will be provided as shift tables

Abnormality criteria based on toxicity grade and normal ranges will be applied to baseline and postbaseline values.

Postbaseline abnormalities will be compared with their corresponding baseline result:

- For toxicity grades, treatment emergent (TE) will be concluded if the postbaseline grade is worse than the baseline grade.
- For abnormalities based on normal range and/or criteria: If the postbaseline value is above the upper limit and the baseline value is below the upper limit (e.g., Normal or Low), then the postbaseline abnormality will be considered TE. The same applies to the postbaseline value being below the lower limit with the baseline value being above the lower limit (e.g., Normal or High).
- If the baseline value is missing, a postbaseline abnormality will always be considered as TE.

Number and percentage of participants with postbaseline clinically important laboratory values and/or markedly abnormal postbaseline values will be presented over time. A listing of clinically important laboratory values will be provided.

The clinically important laboratory findings to be reported are described below:

- AST (U/L): 2x ULN
- ALT (U/L): 2x ULN
- Alkaline phosphate (U/L): 2.5x ULN

Markedly abnormal laboratory findings to be reported are described below:

- AST (U/L): 2x ULN
- ALT (U/L): 2x ULN

- Grade 4 NCI-CTAE
- Decrease in Hemoglobin > 2 grades from baseline and outside normal range

Applicable laboratory results will be graded according to NCI-CTAE version 5.0.

Descriptive statistics and change from baseline analyses of clinical laboratory results will be presented.

Shift tables will be provided summarizing the shift in laboratory values from baseline to over time with respect to abnormality criteria (low, normal, high).

Shift summaries from baseline laboratory value to the worst grade during the study in chemistry and hematology tests with will be presented.

Laboratory criteria for potential Hy's Law cases are defined as:

- Peak aminotransaminases (AT, either ALT or AST) of >3x ULN (Upper Limit of Normal);
- Total bilirubin ≥2x ULN
- Alkaline phosphatase (ALK-P) <2x ULN prior to or on the same date of the first occurrence of total bilirubin ≥2x ULN

Note: data from all the on-treatment (post-baseline) visits are combined to check the above laboratory criteria.

All potential Hy's Law cases based on the laboratory criteria will be presented. Absence of an underlying clinical condition that would explain the laboratory findings will be needed to conclude a true Hy's Law case.

eDISH is an electronic tool for evaluation of Drug-induced Serious Hepatotoxicity. The criteria are the same as Hy's Law, but do not include Criteria 3 above. An eDISH plot will also be created by intervention group.

5.6.4. Vital Signs and Physical Examination Findings

Continuous vital sign parameters including temperature, oxygen saturation, pulse/heart rate, and blood pressure (systolic and diastolic) from physical examination will be summarized at each assessment time point. Change from baseline will be summarized over time. Descriptive statistics (mean, standard deviation, median, minimum and maximum) will be presented.

Incidence of treatment-emergent clinically important/markedly abnormal vital signs during intervention will be summarized for participants who had a baseline assessment and at least 1 postbaseline assessment for that vital sign. Similar rules will be applied for comparing postbaseline abnormalities with corresponding baselines as described in the previous section. A listing of participants with treatment-emergent clinically important/markedly abnormal vital signs will be presented, along with a listing of all vital sign measurements.

5.6.5. Electrocardiogram

The Electrocardiogram (ECG) parameters that will be analyzed is the corrected QT (QTcF) interval. The number and percentage of participants with QTcF interval will be summarized at each scheduled time point. Refer to the following table for summary categories.

Criteria for Abnormal QTcF Values and Changes from Baseline	
QTcF value	<=450
	>450 – 480
	>480 – 500
	>500
QTcF change from baseline	<=30
	>30 – <=60
	> 60

Descriptive statistics and change from baseline will be summarized at each scheduled time point. If ECG measurements are repeated at a visit, they will be averaged. The averaged value will be considered the 'Visit' ECG result. The interpretation of the ECGs as determined by a qualified physician (investigator or qualified designee) will be displayed by the number and percentage of participants meeting the normality criteria. The interpretation will be summarized over time. A listing of clinically relevant ECG abnormalities will also be provided.

5.7. Other Analyses

5.7.1. Pharmacokinetics

For evaluation of PK primary endpoints, PK analyses will be performed on the PK Primary Endpoint Evaluable Analysis Set. All other PK analyses will be performed on the Other PK Evaluable Analysis Set.

The PK assessments that will be performed are defined as follows:

- C_{trough} Observed concentration immediately prior to the next drug administration
- C_{max} Maximum observed concentration
- $AUC_{(D1\text{-}D15)}$ Area under the concentration time curve from Day 1 to Day 15
- $AUC_{(D1\text{-}D8)}$ Area under the concentration time curve from Day 1 to Day 8

The primary PK endpoints are C_{trough} (at steady state in Cycle 4 for all regions other than EU and prior to first dose at Cycle 2 Day 1 for EU only) and $AUC_{(D1\text{-}D15)}$ during Cycle 2. The summary statistics such as geometric mean, coefficient of variation, median, and range will be provided by treatment group. The ratio of geometric means and the corresponding 90% CIs using logarithmic transformation of $C_{trough,}$ and AUC values will be provided. If the ratio of the geometric mean of maximum C_{trough} and AUC are $\geq$ 80% (non-inferiority margin of 20%), amivantamab SC-CF will be considered non-inferior to amivantamab IV. The secondary end point, model-predicted AUC at steady state, will be estimated based on the Population PK modeling. Population PK analysis of serum concentration-time data of amivantamab will be performed using nonlinear mixed-effects

modeling (NONMEM) and may be combined with data from other studies. Details will be provided in a population PK and exposure-response analysis plan and results of the analysis will be presented in a separate report.

Serum samples will be collected for PK and immunogenicity assessments of amivantamab. Plasma samples will be collected for the evaluation of PK of lazertinib. Sampling time points are outlined in Table 3 of study protocol.

Concentrations below the lowest quantifiable concentration or missing data will be labeled as such in the concentration data presentations or statistical analysis system dataset. Concentrations below the lower quantifiable concentration will be treated as zero in the summary statistics.

Descriptive statistics (N, mean, SD, median, range, and CV (%)) will be used to summarize the amivantamab and lazertinib concentration at each nominal time point and for each PK parameter of amivantamab and lazertinib. PK data may be displayed graphically, such as mean +/- SD PK concentrations over time by study treatment.

Amivantamab concentrations will be presented for all participants and by body weight based on the following baseline body weight categories at each time point:

- <80 kg
- ≥ 80 kg

All participants and samples excluded from the analysis will be clearly documented. Participants may be excluded from the PK analysis if their data do not allow for accurate assessment of the PK (e.g., incomplete administration of the study drug; missing information of dosing and sampling times; concentration data not sufficient for PK parameter calculation).

The details of PK analysis plan and the results of the analysis will be presented in a separate report.

5.7.2. Immunogenicity

The incidence of antibodies to amivantamab will be summarized for all participants who receive at least 1 dose of amivantamab and have appropriate samples for detection of antibodies to amivantamab (i.e., participants with at least 1 sample obtained after their first dose of amivantamab).

A listing of participants who are positive for antibodies to amivantamab will be provided. The maximum titers of antibodies to amivantamab will be summarized for participants who are positive for antibodies to amivantamab.

Other immunogenicity analyses may be performed to further characterize the immune responses that are generated.

5.7.3. Pharmacodynamics/Biomarkers

Analyses are planned to explore biomarkers that may be indicative of potential mechanisms of resistance to amivantamab and lazertinib and will use the Biomarkers Population. Correlation of baseline expression levels or changes in expression levels with response or time-to-event endpoints could be used identify resistant subgroups.

Each baseline tumor status may be evaluated by ctDNA NGS analysis, for exploratory purposes, to characterize potential mechanisms of resistance to amivantamab and lazertinib, and to evaluate the presence of mutations across treatment arms, as permitted by local regulations.

Assessment of additional genes or biomarkers (DNA, RNA, or protein) relevant to lung or other cancers and assessment of the mechanism of action or metabolism of study treatments may also be performed in blood samples collected on study to better understand mechanisms of response or resistance to study treatment. Alterations in blood characteristics may be evaluated for correlation with response to study treatment, tumor burden, and disease progression as data warrant.

5.7.4. Pharmacokinetic/Pharmacodynamic Relationships

Pharmacokinetic/pharmacodynamic modeling may be performed, including exploring the relationship between serum concentrations of amivantamab and endpoints of clinical efficacy and safety. If performed, details and results of the analysis will be presented in a separate report.

5.7.5. Health Economics

Time and motion analysis will be performed to assess the healthcare burden impact. Details have been outlined in section 5.4.2.

5.7.6. Definition of Subgroups

The following pre-specified subgroup analyses are to be performed for the efficacy and/or safety endpoints. Additional subgroup analyses may be planned if deemed necessary, provided there is an adequate sample size (i.e., > 20 participants) for each of the subgroups.

Subgroup	Definition of Subgroup
Age	<65 years, >=65 years; <75 years, >=75 years
Sex	Male, Female
Race	Asian, Non-Asian
ECOG performance status	0, 1
History of Smoking	Yes, No
Most recent line of therapy	osimertinib, chemotherapy, osimertinib + chemotherapy
Mutation Type	Exon 19del, Exon 21 L858R

5.8. Independent Data Monitoring Committee

An IDMC will be established. This committee will consist of at least one medical expert in the relevant therapeutic area and at least one statistician; committee membership responsibilities, authorities, and procedures will be documented in its charter. The committee will meet periodically

to review interim data. A first IDMC meeting will be held after the first 20 participants complete 2 cycles of treatment. After the review, the IDMC will make recommendations regarding the continuation of the study. Besides, this committee will also monitor available data on an ongoing basis throughout the study to ensure the continued safety of participants enrolled in this study.

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 List of Abbreviations

ADA	anti-drug antibody
AE	adverse event
ALT/SGPT	alanine aminotransferase
ANCOVA	analysis of covariance
AST/SGOT	aspartate aminotransferase
ATC	anatomic and therapeutic class
AUC	area under the curve
BMI	body mass index
BSA	body surface area
CI	confidence interval
CL	total systemic clearance
Cmax	maximum concentration
CRF	case report form
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
DMC	Data Monitoring Committee
DPS	Data Presentation Specifications
ECG	electrocardiogram
eCRF	electronic case report form
F (%)	absolute SC bioavailability
FAS	full analysis set
FDA	Food and Drug Administration
ICH	International Conference on Harmonisation
IQ	interquartile
IVRS	interactive voice response system
IWRS	interactive web response system
LLOQ	lower limit of quantification
LOCF	last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
MRD	minimum required dilution
NAb	neutralizing antibodies
PD	pharmacodynamic(s)
PI	principal investigator
PK	pharmacokinetic(s)
PP	per protocol
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SMQs	standardised MedDRA queries
TEAE	treatment-emergent adverse event
Tmax	time to maximum concentration
US NCI	United States National Cancer Institute
V	volume distribution
Vz	volume of distribution based on terminal phase
Vz/F	apparent volume of distribution based on terminal phase after extravascular administration
WHO	World Health Organization
WHO-DD	World Health Organization Drug Dictionary

6.2. Appendix 2 Changes to Protocol-Planned Analyses

Not Applicable.

6.3. Appendix 3 Demographics and Baseline Characteristics

The number of participants in each analysis set will be summarized and listed by treatment group, and overall. In addition, the distribution of participants by region, country, and site ID will be presented unless otherwise noted.

Table below presents a list of the demographic variables that will be summarized by treatment group and overall, for the full analysis set.

Continuous Variables:	**Summary Type**
Age (years)	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum).
Weight (< 80 kg and >= 80 kg)	
Height (cm)	
Body Mass Index (BMI) (kg/m^2)	
Categorical Variables	
Age (< 65 years, >= 65 years, <75 years, >= 75 years)	Frequency distribution with the number and percentage of participants in each category.
Race[a] (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, White, Multiple)	
Race (Asian, Non-Asian)	
Ethnicity (Hispanic or Latino, not Hispanic or Latino)	
Baseline ECOG performance status ([0, >=1])	
History of Smoking (Yes, No)	

[a]If multiple race categories are indicated, the Race is recorded as 'Multiple'

The following table presents a list of the baseline characteristics variables that will be summarized by treatment group and overall, for the full analysis set.

Continuous Variables:	**Summary Type**
Time since initial lung cancer diagnosis (months)	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum].
Time since metastatic disease diagnosis (months)	
Number of prior lines of systemic therapy	
Categorical Variables	
Mutation type (Exon 19del, Exon 21 L858R)	Frequency distribution with the number and percentage of participants in each category.
History of brain metastasis (present, absent)	
NSCLC subtype (adenocarcinoma, large cell carcinoma, other)	
Cancer stage at initial diagnosis (0, IA, IB, IIA, IIB, IIIA, IIIB, IIIC, IV)	
Cancer stage at screening (0, IA, IB, IIA, IIB, IIIA, IIIB, IIIC, IV)	
Location of metastasis at screening (bone, liver, brain, lymph node, adrenal gland, lung, other)	
Last prior therapy (osimertinib or chemotherapy)	

6.4. Appendix 4 Protocol Deviations

In general, the following list of major protocol deviations may have the potential to impact participants' rights, safety or well-being, or the integrity and/or result of the clinical study. Participants with major protocol deviations will be identified prior to database lock and the participants with major protocol deviations will be summarized by category.

- Developed withdrawal criteria but not withdrawn

- Enrolled but did not satisfy criteria
- Received a disallowed concomitant treatment
- Received wrong treatment or incorrect dose
- Other

A listing of all major protocol deviations including subject ID, type of deviation, and reason will be provided.

6.5. Appendix 5 Prior and Concomitant Medications

Prior and Concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO-DD). Prior medications are defined as any therapy used before the day of first dose (partial or complete) of study intervention. Concomitant medications are defined as any therapy used on or after the same day as the first dose of study intervention, including those that started before and continue after the first dose of study intervention.
Summaries of concomitant medications will be presented by ATC level/preferred terms for each treatment group and overall for the full analysis set. The proportion of participants who receive each concomitant medication will be summarized as well as the proportion of participants who receive at least 1 concomitant medication.

The number and percentage of participants who received prior systemic therapy will be summarized. The incidence of prior systemic therapy will be presented by ATC level/preferred terms.

Prior medications will be summarized by ATC level/preferred terms and treatment group.

6.6. Appendix 6 Medical History

Medical history collected at screening visit will be summarized by system-organ class and preferred term for each treatment group and overall, for the Full Analysis Set.

6.7. Appendix 7 Adverse Events of Special Interest

Adverse events of special interest are defined as follows:

AE Clinical Importance Category	**Preferred Term**
Infusion Related Reaction	INFUSION RELATED REACTION
Rash	ACNE ACNE CONGLOBATA ACNE CYSTIC ACNE FULMINANS ACNE PUSTULAR ACNE VARIOLIFORMIS ACUTE GENERALISED EXANTHEMATOUS PUSTULOSIS DERMATITIS DERMATITIS ACNEIFORM DERMATITIS EXFOLIATIVE DERMATITIS INFECTED DRUG ERUPTION EPIDERMOLYSIS ERYTHEMA ERYTHEMA MULTIFORME EXFOLIATIVE RASH FOLLICULITIS HERPES GESTATIONIS IMPETIGO HERPETIFORMIS MACULE MUCOCUTANEOUS RASH NODULAR RASH PALMAR ERYTHEMA PAPULE PERINEAL RASH PRIDE SYNDROME PUSTULE RASH RASH ERYTHEMATOUS RASH FOLLICULAR RASH MACULAR RASH MACULO-PAPULAR RASH MACULOVESICULAR RASH MORBILLIFORM RASH PAPULAR RASH PRURITIC RASH PUSTULAR RASH VESICULAR SJS-TEN OVERLAP SKIN EXFOLIATION SKIN LESION STEVENS-JOHNSON SYNDROME TOXIC EPIDERMAL NECROLYSIS TOXIC SKIN ERUPTION
Peripheral Edema	FLUID OVERLOAD FLUID RETENTION GENERALISED OEDEMA HYPERVOLAEMIA

	OEDEMA OEDEMA PERIPHERAL
Venous Thromboembolic Events	PULMONARY EMBOLISM DEEP VEIN THROMBOSIS
Interstitial Lung Disease	ACUTE INTERSTITIAL PNEUMONITIS INTERSTITIAL LUNG DISEASE PNEUMONITIS

Adverse events of special interest defined as follows:

AE Special Interest Category	**Search Criteria Category**	**Preferred Term**
NAIL BED DISORDER	Nail Bed Disorder (PT grouping)	NAIL BED INFECTION NAIL INFECTION PARONYCHIA
	Nail and nail bed conditions (HLT grouping)	NAIL AND NAIL BED CONDITIONS (EXCL INFECTIONS AND INFESTATIONS)
STOMATITIS	Stomatitis (PT grouping)	APHTHOUS ULCER LIP EROSION LIP ULCERATION MOUTH ULCERATION ORAL MUCOSA EROSION PALATAL ULCER STOMATITIS STOMATITIS HAEMORRHAGIC STOMATITIS NECROTISING
DRY SKIN	Dry Skin (PT grouping)	DRY SKIN ECZEMA SKIN FISSURES XERODERMA XEROSIS
PRURITUS	Pruritus (PT grouping)	PRURITUS

6.8. Appendix 8 Laboratory Toxicity Grading

The grading scale use for lab assessments is based on 'Common Terminology Criteria for Adverse Events (CTCAE) V5.0

If a laboratory value falls within the grading as specified below but also within the local laboratory normal limits, the value is considered to be normal and will be reset to grade 0.

Pre-baseline measurements will use the same grading ranges as applied to baseline measurements. In case a test has two sets of ranges – one for baseline normal and one for baseline abnormal, the one for baseline normal will be applied for all measurements taken pre-baseline and on baseline.

Text in gray italic in the table is present in the grading scale but is not applied by Janssen when grading lab data.

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Janssen implementation notes
Blood and lymphatic system disorders					
Anemia	Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	Hemoglobin (Hgb) <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	Hemoglobin (Hgb) <8.0 g/dL; <4.9 mmol/L; <80 g/L; *transfusion indicated*	*Life-threatening consequences. urgent intervention indicated*	Clinical signs and symptoms are not taken into consideration for grading.
Leukocytosis	-	-	>100,000/mm3; >100 x 10e9 /L	*Clinical manifestations of leukocytosis; urgent intervention indicated*	Clinical signs and symptoms are not taken into consideration for grading; Added ranges in SI unit (x 10e9 /L)
Investigations					
Activated partial thromboplastin time prolonged	>ULN - 1.5 x ULN	>1.5 - 2.5 x ULN	>2.5 x ULN; *bleeding*	-	Clinical signs and symptoms are not taken into consideration for grading.
Alanine aminotransferase increased	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	Ranges defined for "abnormal baseline" are applied only if baseline > ULN. If baseline < LLN, then ranges for "normal baseline" are applied.
Alkaline phosphatase increased	>ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal	>2.5 - 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	Ranges defined for "abnormal baseline" are applied only if baseline > ULN. If baseline < LLN, then ranges for "normal baseline" are applied.
Aspartate aminotransferase increased	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	Ranges defined for "abnormal baseline" are applied only if baseline > ULN. If baseline < LLN, then ranges for "normal baseline" are applied.
Blood bilirubin increased	>ULN - 1.5 x ULN if baseline was normal;	>1.5 - 3.0 x ULN if baseline was normal;	>3.0 - 10.0 x ULN if baseline was normal;	>10.0 x ULN if baseline was normal;	Ranges defined for "abnormal baseline" are

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Janssen implementation notes
	> 1.0 - 1.5 x baseline if baseline was abnormal	>1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 10.0 x baseline if baseline was abnormal	>10.0 x baseline if baseline was abnormal	applied only if baseline > ULN. If baseline < LLN, then ranges for "normal baseline" are applied.
CD4 lymphocytes decreased	<LLN - 500/mm3; <LLN - 0.5 x 10e9 /L	<500 - 200/mm3; <0.5 - 0.2 x 10e9 /L	<200 - 50/mm3; <0.2 x 0.05 - 10e9 /L	<50/mm3; <0.05 x 10e9 /L	
Cholesterol high	>ULN - 300 mg/dL; >ULN - 7.75 mmol/L	>300 - 400 mg/dL; >7.75 - 10.34 mmol/L	>400 - 500 mg/dL; >10.34 - 12.92 mmol/L	>500 mg/dL; >12.92 mmol/L	
CPK increased	>ULN - 2.5 x ULN	>2.5 x ULN - 5 x ULN	>5 x ULN - 10 x ULN	>10 x ULN	
Creatinine increased	Creatine Kinase >ULN - 1.5 x ULN	Creatine Kinase >1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	Creatine Kinase >3.0 x baseline; >3.0 - 6.0 x ULN	Creatine Kinase >6.0 x ULN	
Fibrinogen decreased	<1.0 - 0.75 x LLN; if abnormal, <25% decrease from baseline	<0.75 - 0.5 x LLN; if abnormal, 25 - <50% decrease from baseline	<0.5 - 0.25 x LLN; if abnormal, 50 - <75% decrease from baseline	<0.25 x LLN; if abnormal, 75% decrease from baseline; absolute value <50 mg/dL	Ranges defined for "abnormal" are applied only on values < LLN. Grade 0 will be assigned to values > ULN.
GGT increased	>ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal	>2.5 - 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	Ranges defined for "abnormal baseline" are applied only if baseline > ULN. If baseline < LLN, then ranges for "normal baseline" are applied.
Haptoglobin decreased	<LLN	-	-	-	
Hemoglobin increased	Increase in >0 - 2 g/dL; Increase in >0 - 20 g/L	Increase in >2 - 4 g/dL; Increase in >20 - 40 g/L	Increase in >4 g/dL; Increase in >40 g/L	-	The increase indicates the level of increase above normal (above ULN). Applied as, e.g. grade 1 (g/dL): >ULN – ULN+2 g/dL; Added ranges in SI unit (g/L).
INR increased	>1.2 - 1.5; *>1 - 1.5 x baseline if on anticoagulation; monitoring only indicated*	>1.5 - 2.5; *>1.5 - 2.5 x baseline if on anticoagulation; dose adjustment indicated*	>2.5; *>2.5 x baseline if on anticoagulation; bleeding*	-	Concomitant therapy or clinical signs and symptoms are not taken into consideration for grading.

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Janssen implementation notes
Lipase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN; *>2.0 - 5.0 x ULN and asymptomatic*	>2.0 - 5.0 x ULN with signs or symptoms; *>5.0 x ULN and asymptomatic*	>5.0 x ULN and with signs or symptoms	"Asymptomatic" ranges are not taken into consideration for grading, i.e. worst case grading is applied.
Lymphocyte count decreased	<LLN - 800/mm3; <LLN - 0.8 x 10e9/L	<800 - 500/mm3; <0.8 - 0.5 x 10e9 /L	<500 - 200/mm3; <0.5 - 0.2 x 10e9 /L	<200/mm3; <0.2 x 10e9 /L	
Lymphocyte count increased	-	>4000/mm3 - 20,000/mm3; >4 - 20 x 10e9 /L	>20,000/mm3; >20 x 10e9 /L	-	Added ranges in SI unit (x 10e9 /L).
Neutrophil count decreased	<LLN - 1500/mm3; <LLN - 1.5 x 10e9 /L	<1500 - 1000/mm3; <1.5 - 1.0 x 10e9 /L	<1000 - 500/mm3; <1.0 - 0.5 x 10e9 /L	<500/mm3; <0.5 x 10e9 /L	Both Neutrophils and segmented neutrophils are graded using these criteria.
Platelet count decreased	<LLN - 75,000/mm3; <LLN - 75.0 x 10e9 /L	<75,000 - 50,000/mm3; <75.0 - 50.0 x 10e9 /L	<50,000 - 25,000/mm3; <50.0 - 25.0 x 10e9 /L	<25,000/mm3; <25.0 x 10e9 /L	
Serum amylase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN; *>2.0 - 5.0 x ULN and asymptomatic*	>2.0 - 5.0 x ULN *with signs or symptoms; >5.0 x ULN and asymptomatic*	>5.0 x ULN *and with signs or symptoms*	"Asymptomatic" ranges are not taken into consideration for grading, i.e. worst case grading is applied.
White blood cell decreased	<LLN - 3000/mm3; <LLN - 3.0 x 10e9 /L	<3000 - 2000/mm3; <3.0 - 2.0 x 10e9 /L	<2000 - 1000/mm3; <2.0 - 1.0 x 10e9 /L	<1000/mm3; <1.0 x 10e9 /L	
Metabolism and nutrition disorders					
Acidosis	pH <normal, but >=7.3	-	pH <7.3	*Life-threatening consequences*	pH <normal is implemented as pH <LLN. Clinical signs and symptoms are not taken into consideration for grading.
Alkalosis	pH >normal, but <=7.5	-	pH >7.5	*Life-threatening consequences*	pH >normal is implemented as pH >ULN. Clinical signs and symptoms are not taken into consideration for grading.

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Janssen implementation notes
Hypercalcemia	Corrected serum calcium of >ULN - 11.5 mg/dL; >ULN - 2.9 mmol/L; Ionized calcium >ULN - 1.5 mmol/L	Corrected serum calcium of >11.5 - 12.5 mg/dL; >2.9 - 3.1 mmol/L; Ionized calcium >1.5 - 1.6 mmol/L; *symptomatic*	Corrected serum calcium of >12.5 - 13.5 mg/dL; >3.1 - 3.4 mmol/L; Ionized calcium >1.6 - 1.8 mmol/L; *hospitalization indicated*	Corrected serum calcium of >13.5 mg/dL; >3.4 mmol/L; Ionized calcium >1.8 mmol/L; *life-threatening consequences*	Clinical signs and symptoms are not taken into consideration for grading.
Hyperkalemia	Potassium >ULN - 5.5 mmol/L	Potassium >5.5 - 6.0 mmol/L; *intervention initiated*	Potassium >6.0 - 7.0 mmol/L; *hospitalization indicated*	Potassium >7.0 mmol/L; *life-threatening consequences*	Clinical signs and symptoms are not taken into consideration for grading.
Hypermagnesemia	Magnesium >ULN - 3.0 mg/dL; >ULN - 1.23 mmol/L	-	Magnesium >3.0 - 8.0 mg/dL; >1.23 - 3.30 mmol/L	Magnesium >8.0 mg/dL; >3.30 mmol/L; *life-threatening consequences*	Clinical signs and symptoms are not taken into consideration for grading.
Hypernatremia	Sodium >ULN - 150 mmol/L	Sodium >150 - 155 mmol/L; *intervention initiated*	Sodium >155 - 160 mmol/L; *hospitalization indicated*	Sodium >160 mmol/L; *life-threatening consequences*	Clinical signs and symptoms are not taken into consideration for grading.
Hypertriglyceridemia	Triglycerides 150 mg/dL - 300 mg/dL; 1.71 mmol/L - 3.42 mmol/L	Triglycerides >300 mg/dL - 500 mg/dL; >3.42 mmol/L - 5.7 mmol/L	Triglycerides >500 mg/dL - 1000 mg/dL; >5.7 mmol/L - 11.4 mmol/L	Triglycerides >1000 mg/dL; >11.4 mmol/L; *life-threatening consequences*	Clinical signs and symptoms are not taken into consideration for grading.
Hypoalbuminemia	Albumin <LLN - 3 g/dL; <LLN - 30 g/L	Albumin <3 - 2 g/dL; <30 - 20 g/L	Albumin <2 g/dL; <20 g/L	*Life-threatening consequences; urgent intervention indicated*	Clinical signs and symptoms are not taken into consideration for grading.
Hypocalcemia	Corrected serum calcium of <LLN - 8.0 mg/dL; <LLN - 2.0 mmol/L; Ionized calcium <LLN - 1.0 mmol/L	Corrected serum calcium of <8.0 - 7.0 mg/dL; <2.0 - 1.75 mmol/L; Ionized calcium <1.0 - 0.9 mmol/L;	Corrected serum calcium of <7.0 - 6.0 mg/dL; <1.75 - 1.5 mmol/L; Ionized calcium <0.9 - 0.8 mmol/L;	Corrected serum calcium of <6.0 mg/dL; <1.5 mmol/L; Ionized calcium <0.8 mmol/L;	Clinical signs and symptoms are not taken into consideration for grading.

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Janssen implementation notes
		symptomatic	*hospitalization indicated*	*life-threatening consequences*	
Hypoglycemia	Glucose <LLN - 55 mg/dL; <LLN - 3.0 mmol/L	Glucose <55 - 40 mg/dL; <3.0 - 2.2 mmol/L	Glucose <40 - 30 mg/dL; <2.2 - 1.7 mmol/L	Glucose <30 mg/dL; <1.7 mmol/L; *life-threatening consequences; seizures*	Clinical signs and symptoms are not taken into consideration for grading. Urine glucose is not graded.
Hypokalemia	*Potassium <LLN - 3.0 mmol/L*	*Symptomatic with* Potassium <LLN - 3.0 mmol/L; intervention indicated	Potassium <3.0 - 2.5 mmol/L; *hospitalization indicated*	Potassium <2.5 mmol/L; *life-threatening consequences*	"Symptomatic" ranges are applied for grade 2, grade 1 not assigned, i.e. worst case applied. Clinical signs and symptoms are not taken into consideration for grading of grade 3 and 4.
Hypomagnesemia	Magnesium <LLN - 1.2 mg/dL; <LLN - 0.5 mmol/L	Magnesium <1.2 - 0.9 mg/dL; <0.5 - 0.4 mmol/L	Magnesium <0.9 - 0.7 mg/dL; <0.4 - 0.3 mmol/L	Magnesium <0.7 mg/dL; <0.3 mmol/L; *life-threatening consequences*	Clinical signs and symptoms are not taken into consideration for grading.
Hyponatremia	Sodium <LLN - 130 mmol/L	*Sodium 125-129 mmol/L and asymptomatic*	*Sodium 125-129 mmol/L symptomatic; 120-124 mmol/L regardless of symptoms* Sodium <130-120 mmol/L	Sodium <120 mmol/L; *life-threatening consequences*	Clinical signs and symptoms are not taken into consideration for grading. Worst case ("<130-120 mmol/L" for grade 3 added by Janssen) is applied across grade 2/3 ranges: 120-129 mol/L assigned to grade 3, grade 2 not used.
Renal and urinary disorders					
Proteinuria	1+ proteinuria; urinary protein ≥ULN - <1.0 g/24 hrs; urinary protein ≥ULN - <1000 mg/day	**Adult:** 2+ and 3+ proteinuria; urinary protein 1.0 - <3.5 g/24 hrs;	**Adult:** 4+ proteinuria; urinary protein >=3.5 g/24 hrs;	-	In case both 24-h urine collection and dipstick are collected, then worst case is taken, as opposed to having 24-h urine

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Janssen implementation notes
		urinary protein 1000 - <3500 mg/day **Pediatric:** Urine P/C (Protein/Creatinine) ratio 0.5 - 1.9; Urine P/C (Protein/Creatinine) 56.5 – 214.7 g/mol	urinary protein >=3500 mg/day; **Pediatric:** Urine P/C (Protein/Creatinine) ratio >1.9; Urine P/C (Protein/Creatinine) >214.7 g/mol		collection take precedence over dipstick. Added ranges in SI unit for urinary protein (mg/day) and for urine P/C (g/mol). Pediatric grading is applied to age range [0-18]. Adult grading is applied for ages [>18].

* Grade 0 is assigned to a lab assessment when the lab test is described in the table, but the lab value is not assigned a grade 1 or higher.

7. REFERENCES

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