Janssen Research & Development

Statistical Analysis Plan

Subcutaneous Methotrexate, Oral Dexamethasone or Oral Montelukast for the Prevention of Infusion Related Reaction Associated with Amivantamab, an EGFR-MET bispecific antibody, Among Post-osimertinib Treated EGFRm NSCLC; SKIPPirr, a Phase 2 Study

Protocol 61186372NSC2005; Phase 2

JNJ-61186372 (amivantamab)

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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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1. INTRODUCTION

This is a proof-of-concept open-label, multicenter study in participants with EGFR Exon 19 deletion or L858R mutated NSCLC who have progressed on or after osimertinib and on or after platinum-based chemotherapy, who may benefit from lazertinib and IV amivantamab combination therapy.

The purpose of the statistical analysis plan (SAP) is to lay out key elements including definitions and statistical methods for the planned analyses for the primary, secondary, safety, and other endpoints.

1.1. Objectives

Primary objective:

- To separately assess the potential of dexamethasone, montelukast and methotrexate administration prior to the initial IV amivantamab infusion to decrease the incidence and/or severity of IRR when amivantamab is given in combination with oral lazertinib.

Secondary objectives:

- To evaluate incidences and severity of individual IRR signs and symptoms (chills, dyspnea, flushing, nausea, chest discomfort, vomiting, tachycardia, hypotension, fever).
- To evaluate incidences of all non-IRR AEs.
- To measure IV amivantamab infusion related times.
- To estimate the anti-tumor activity of IV amivantamab and lazertinib following pre-medication with study treatment.

1.2. Study Design

This is a proof-of-concept open-label, multicenter study in participants with EGFR Exon 19 deletion or L858R mutated NSCLC who have progressed on or after osimertinib, and on or after platinum-based chemotherapy, who may benefit from lazertinib and IV amivantamab combination therapy. In the study, all participants will receive standard prophylaxis with antihistamine, antipyretic, and glucocorticoid as used in clinical trials of amivantamab and lazertinib.

There are four cohorts in the study.

Cohort A: Participants will be administered oral dexamethasone (4 mg) twice a day (8 mg total daily dose) on Day -1 (Cycle 1) prior to lazertinib and IV amivantamab combination therapy in addition to all other standard premedication.

Cohort A2: Participants will be administered oral dexamethasone (8 mg) twice a day (16 mg total daily dose) on Day -2 and -1 (Cycle 1) and 8 mg approximately one hour prior to the start of the infusion of IV amivantamab on Cycle 1 Day 1.

Cohort B: Participants will be administered oral montelukast (10 mg) in the morning on Days -4, -3, -2, -1, and C1D1 (5 doses total) prior to lazertinib and IV amivantamab combination therapy.

Cohort C: Participants will be administered a single dose of 25 mg subcutaneous (SC) methotrexate on any day between Days -7 and Day -3 (Cycle 1) prior to lazertinib and IV amivantamab combination therapy.

Within each cohort, a total of up-to 40 subjects treated with amivantamab and lazertinib are planned with up-to 16 subjects based on Simon's optimal two stage design and up-to 24 subjects for cohort expansion stage. In the Simon's two stage design portion of each cohort, six subjects are planned for Stage 1 and 10 subjects are planned for Stage 2. If both Cohorts A and A2 have positive results in Stage 1, only one cohort with dexamethasone (Cohort A or A2) would move on to the subsequent stages. Hence a total of up-to 126 subjects treated with amivantamab and lazertinib are planned in this study.

Sequential enrollment will be applied throughout the study (No two or more cohorts will be open simultaneously). The study will start from Stage 1 in the order of enrolling cohort A, B, C and then A2. To avoid enrollment interruption, it is permissible to start Stage 2 of a cohort before Stage 1 of all cohorts is complete. The determination of which cohorts can move to Stage 2 and which cohort will be open for enrollment will be decided by a Study Evaluation Team (SET) considering Simon's two stage design guidance, data availability and other operational definitions.

2. STATISTICAL HYPOTHESES

Hypothesis

Through prophylactic treatment with enhanced dexamethasone, montelukast, or methotrexate pretreatment, the incidence of IV amivantamab IRRs on Cycle 1 Day 1 will be reduced: $H_0 : IRR \geq 0.67 \; vs. \; H_1 : IRR < 0.67$

3. SAMPLE SIZE DETERMINATION

Simon's two-stage design (Simon, 1989) is used separately for each cohort. Details of the design are below.

Stage 1: Treat up to 6 patients

- If number of patients with IRR $\geq$ 4 (out of 6), the cohort stops at Stage 1.
- Otherwise, move on to Stage 2.

Stage 2: Treat up to10 additional patients

- Reject the null hypothesis in that cohort if number of patients with IRR $\leq$ 8 (out of 16), the cohort will be declared promising in lowering IRR.

CCI [redacted]

- CCI [redacted]

[redacted]

If the null hypothesis can be rejected in a cohort, that cohort can be expanded by adding up to 24 additional patients (up to 40 patients total per expanded cohort). SET will determine if a cohort will move into Stage 2 and to the expansion stage and the sample size of the expansion stage based on accrued data.

3.1. Randomization and Blinding

This is an open-label study. No blinding of treatment will be performed.

Within each cohort, there is one single arm, hence no randomization is needed.

4. POPULATIONS (ANALYSIS SETS) FOR ANALYSIS

Analysis Sets	Description
Prophylaxis Analysis set	The prophylaxis analysis set includes all subjects received at least one dose of prophylaxis treatment prior to the first administration of amivantamab and lazertinib.
Per Protocol Analysis Set	The per protocol analysis set includes all subjects who had received all prophylaxis treatment based on schedule and had received the administration of amivantamab and Lazertinib on C1D1
Safety Analysis Set	The safety analysis set includes all participants who received at least 1 administration of amivantamab and lazertinib
Response Evaluable Analysis Set	The response evaluable analysis set is defined as all participants who receive at least one dose of amivantamab and lazertinib and who have at least one postbaseline disease assessments, clinical progression, or died due to disease progression before the first postbaseline disease assessment

5. STATISTICAL ANALYSES

5.1. General Considerations

All analyses will be conducted by cohort and for safety analysis set unless otherwise specified.

5.1.1. Visit Windows

Visit windowing will be based on study phases and cycles. Unless otherwise specified, data to be analyzed or presented over time will be presented by cycle, day and time point (as appropriate) that are recorded in eCRF.

5.1.2. Study Day/Relative Day

Study day or relative day is defined as:

- Reference date (Day 1) = first dose date of amivantamab and lazertinib.

- Study Day = assessment date – reference date + 1 for assessment performed on or after the reference date; assessment date – reference date for assessment performed before the reference date.

There is no 'Day 0'.

5.1.3. Pooling Algorithm for Analysis Centers

Data from all study centers will be combined for statistical analyses.

5.1.4. Study Treatment and Study Drug

For ANALYSIS purposes of this study, 'study treatment' refers to the combination of Amivantamab and Lazertinib. Study drug refers to each study agent: either amivantamab or lazertinib.

Prophylaxis treatments (oral dexamethasone, oral montelukast, and SC methotrexate) provided by Sponsor will be referred as such.

5.1.5. Study drug Dosing Date

Study drug dosing date is the date on which a subject actually received amivantamab and lazertinib (partial or complete) and will be recorded in the study drug administration dataset, Dosage Administration page of the CRF.

For subjects who receive the amivantamab and lazertinib, the first administration date is defined as the earliest date of non-zero dose of amivantamab and lazertinib. The last study drug date is defined as the latest date of non-zero dose of amivantamab and lazertinib.

5.1.6. Baseline Measurement

Unless specified otherwise, the baseline value is defined as the last non-missing value collected before or on the date of administration of the first dose of amivantamab and lazertinib unless it is identifiable by time that the value is after the first dose of amivantamab and lazertinib.

5.1.7. Imputation of Missing Data

Unless specified otherwise, no data imputation will be applied for missing safety and efficacy evaluations. For analysis and reporting purposes, partial dates in adverse event (AE onset date; AE end date), concomitant therapies (start date; end date), prior diagnosis date, and start date of subsequent anti-tumor therapy will be imputed as detailed below.

5.1.7.1. Adverse Event Start and End Date

Adverse Event Start Date

If the onset date of an adverse event is completely or partially missing, the following imputation rules will be used.

- When month and year are present, and the day is missing:
    - If the onset month and year are the same as the month and year of first dosing date, the day of first dosing or the day-component of the AE end date (possibly imputed) is imputed, whichever is earlier;
    - If the onset month and year are not the same as the month and year of first treatment with study drug, the first day of the month is imputed.

- When only a year of the onset date is present:
    - If the onset year is the same as the year of first treatment with study drug:
        - If AE end date is available and is prior to first dosing date, the day and month of AE end date are imputed.
        - Otherwise, the day and month of the first dosing date are imputed.
    - If the onset year is different from the year of first treatment with study drug, the 1st of January is imputed.
- If the onset date is completely missing, the first dosing date is imputed as the onset date.

No imputation will be done for partial or missing AE onset time.

Adverse Event End Date

If the end date of an adverse event is completely or partially missing, the following imputation rules will be used.

- If month and year are present and the day of the month is missing, the last day of the month is imputed.
- If only a year is present, the 31st of December is used.

After the imputation, if the imputed date is later than the date of death (if available) after imputation, the date of death will be used as the imputed date.

5.1.7.2. Partial Initial/ Metastatic Disease Diagnosis Date

For partially missing initial or metastatic diagnosis dates, the following imputation rules will be applied. If the date is completely missing, no imputation will be performed.

- If only the day is missing, impute day with 1.
- If both the day and month are missing, impute with January 1.

If the imputed date of metastatic disease diagnosis is before the date of initial disease diagnosis, set the date of metastatic disease diagnosis as the date of initial disease diagnosis. If the imputed

date of initial or metastatic disease diagnosis is on or after the first treatment date, further adjust the imputed start date as the day before the first treatment date.

5.1.7.3. Partial Subsequent Anticancer Therapy Start Date

If year or month of subsequent anticancer therapy start date is missing or no components of the start date are present, no imputation will be performed.

If only the day is missing, the following steps apply:

If the month and year of the start date are the same as the month and year of last dosing date, the day of last dosing date or the day-component of the stop date of subsequent anticancer therapy is imputed, whichever is earlier.

If the start month and year are not the same as the month and year of last dosing date, the first day of the month is imputed.

No imputation will be applied for missing or partial subsequent anticancer therapy end date.

5.1.7.4. Prior Anticancer Therapy Start/ End Date

In case of partially missing dates, the imputation will be done as follows.

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

Otherwise, the following rules will be applied to impute partially missing dates (start date, stop date). If only the day is missing, the 15th day of the month will be used. If both the day and month are missing, the 30th of June will be used.

If the imputed start date is after minimum of first dosing date and anticancer therapy end date, further adjust the imputed start date as minimum of the day prior to first dosing date and anticancer therapy end date; Also adjust the imputed therapy end date so that it is on or after therapy start date.

5.1.7.5. Missing/Partial Death Date

If date is completely missing, no imputation will be made. Otherwise, the following rules will be applied

- If only year is present, but month and day are missing, January 1st will be used.
- If only the day is missing, impute day with 1.

If the imputed death date is on or before the last date that the subject is known to be alive, the last known alive date + 1 will be used.

5.1.8. Other General Considerations

5.1.8.1. Relative Dose Intensity

The relative dose intensity (%) is the ratio of total dose received (mg) and total dose prescribed (mg).

5.2. Participant Dispositions

The following disposition information will be summarized by cohort based on safety analysis set:

Participants who received study treatment

Participants who discontinued study treatment

Reason for discontinuation of study treatment

Participants who terminated study prematurely

Reason for termination of study

A listing of participants will be provided for the following categories:

Participants who discontinued study treatment

Participants who terminated study prematurely

This listing will include subject ID, assigned dose/cohort, date of treatment discontinuation, study day of last dose, reason for discontinuation as well as the specific adverse events (MedDRA preferred term/verbatim term) if discontinuation due to AEs.

5.3. Time and Motion

To evaluate medical resource utilization, participant chair time, treatment room time, and active HCP time including drug preparation, treatment administration, and post-treatment monitoring are collected at each visit of cycle 1. These measurements are summarized by visit.

5.4. Primary Endpoint Analysis

5.4.1. Definition of Endpoint

The primary endpoint is the rate of IRR occurring on C1D1, which is defined as IRR events with onset time within 24 hours of the start of the first amivantamab infusion and prior to the start of amivantamab infusion on Cycle 1 Day 2 if there is Cycle 1 Day 2 infusion of amivantamab. If no Cycle 1 Day 2 infusion of amivantamab, IRR events will be counted as occurring on C1D1 if the onset time of an IRR is within 24 hours of the first amivantamab infusion.

5.4.2. Analysis Methods

Analysis of IRR will be based on safety analysis set. The proportion of subjects who have an IRR within the specified period along with its 90% and 95% exact confidence intervals (CIs) will be calculated for each cohort. The null hypothesis is that the IRR is greater than or equal to 67% for each cohort, which will be rejected if the upper bound of the 90% CI is less than 67%.

As sensitivity analysis, analysis per protocol analysis set will be performed as well.

5.5. Secondary Endpoint Analyses

Only IRR-related and efficacy secondary endpoints are described in this section. Other secondary endpoints such as non-IRR AEs will be included in safety analyses section 5.6.

5.5.1. Objective Response Rate (ORR)

5.5.1.1. Definition

Tumor response will be reported by the investigator in the CRF according to RECIST v1.1. A response of partial response or complete response must be confirmed by repeat assessments ≥4 weeks from the initial observation. For a response to qualify as stable disease, follow-up measurements must have met the stable disease criteria at least once at a minimum interval not less than 6 weeks after the first dose of study agent.

ORR is defined as the proportion of participants who achieve either a complete response or partial response, as defined by the investigator using 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.

Analysis of ORR with confirmation will be using safety analysis set and response evaluable analysis set. Best response of PR or CR, regardless of confirmation will be summarized as well.

5.5.1.2. Analysis Methods

The observed ORR and its 95% 2-sided exact confidence interval will be presented for each cohort and combined cohorts in the response evaluable analysis set.

5.5.2. Duration of Response (DOR)

5.5.2.1. Definition

DOR is defined as the time from the date of first documented response (PR or CR) until the date of documented progression or death, whichever comes first, for participant who have PR or CR. 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 be until the PFS censoring time. Participants who started a subsequent anticancer therapy in the absence of progression will be censored at the last disease assessment before the start of subsequent therapy.

5.5.2.2. Analysis Methods

A Kaplan-Meier plot for duration of response and median duration of response with 95% confidence interval (calculated from the Kaplan-Meier estimate) will be presented.

5.5.3. Rates and severity of individual IRR signs and symptoms on C1D1 and up to the end of the third cycle

5.5.3.1. Definitions

Individual IRR signs and symptoms such as chills, dyspnea, flushing, nausea, chest discomfort, vomiting, tachycardia, hypotension, and fever captured through eCRF will be analyzed.

Similar to IRR on C1D1, IRR signs/symptoms on C1D1 include those within 24 hours of the start of the 1st amivantamab infusion and prior to the 2nd infusion on C1D2.

5.5.3.2. Analysis Methods

The rate of subjects with each of the individual IRR signs and symptoms during Cycle 1 Day 1 will be summarized in total and by severity (all toxicity grade levels, grade level ≥ 2, and grade level ≥ 3). The 95% exact CI will be presented.

Similar summary will be presented for individual IRR signs and symptoms following subsequent administrations up to the end of the third cycle.

A listing will be created for IRRs with occurrences associated with infusions after C1D1.

5.5.4. Rates and severity of IRRs following subsequent administrations

5.5.4.1. Analysis Methods

The rate of subjects with IRRs following subsequent administrations and its 95% exact CI will be presented and by severity (all toxicity grade levels, grade level ≥ 2, and grade level ≥ 3).

5.5.5. Duration of infusion time

5.5.5.1. Definition

Three durations of infusion time are to be analyzed: pre-amivantamab infusion medications on C1D1, IV amivantamab infusion over time, and post-amivantamab infusion medications on C1D1.

5.5.5.2. Analysis Methods

The descriptive summary of amivantamab infusion time, including the median duration and its 95% CI, will be presented. The proportion of participants completing their amivantamab infusion within 4 hours will be presented.

The infusion time of both pre- and post-amivantamab medications will be listed by medication.

5.5.5.3. Analysis Methods

5.6. Safety Analyses

All safety analyses will be based on the safety analysis set, i.e., subjects dosed with amivantamab and lazertinib, unless otherwise specified.

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

5.6.1.1. Amivantamab and Lazertinib Combination

All the exposure information will be summarized based on safety analysis set, and for each study drug.

Study 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 study treatment will be presented in months by treatment group.

The total number of administration cycles of amivantamab received for each participant will be summarized by descriptive statistics. Cumulative duration of amivantamab will be provided by cycle (≥1 cycle, ≥2 cycles, …). Total number of amivantamab infusion and the total dose of amivantamab for each participant will be summarized by descriptive statistics.

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. Cumulative duration of lazertinib will also be provided by month (≥1 month, ≥2 months, …). Total dose administrated for lazertinib will be summarized by descriptive statistics.

The number of interruptions during the amivantamab infusion 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 and reason for cycle delay will be summarized.

5.6.1.2. Prophylaxis Treatments (Dexamethasone, Montelukast or Methotrexate)

The number of administrations receiving each of the prophylaxis treatments and the total dose will be summarized by cohort.

In case there are study participants who are dosed with prophylaxis treatment but do not receive study drug (amivantamab and lazertinib), a listing will be created.

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).

Though any AE occurring at or after the initial administration of any study intervention (prophylaxis or amivantamab/lazertinib) through the day of last dose plus 30 days, or until the start of subsequent anticancer therapy (if earlier), is defined treatment emergent by protocol, for analysis purposes, only those occurring at or after the initial administration of amivantamab and lazertinib, will be referred as treatment emergent (TEAEs). AEs occurring at or after prophylaxis

treatment but before the initial administration of amivantamab and lazertinib will be referred as prophylaxis treatment emergent (PTEAEs).

PTEAEs will be summarized and listed separately with more details provided in Data Presentation Plan (DPS).

Henceforth, the adverse event analysis is specific to TEAEs unless otherwise specified.

In case of missing/partial onset date, if the event occurs on the day of the initial administration of study treatment, and either event time or time of administration are missing, then the event will be assumed to be TEAE. 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 treatment based on partial onset date or resolution date. For each adverse event, the number and percentage of participants who experience at least 1 occurrence of the given event will be summarized by cohort.

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. Treatment Emergent Adverse Events

An overview of TEAEs reported through the study will be provided. The overview will include summaries of participants with TEAEs, with TEAEs related to study drug, with TEAEs of maximum toxicity grade of 1 to 5, Serious TEAEs, TEAEs leading to discontinuation of any study drug, and deaths due to TEAE.

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

The relationship of a TEAE to study drug (amivantamab or lazertinib) is based on the investigators' assessment.

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

Incidence (%) of TEAEs leading to study drug/dose reduction will be summarized respectively by SOC and PT. 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

Incidence (%) of TEAEs leading to study drug discontinuation will be summarized by SOC and PT. 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.

5.6.2.2. Adverse Events of Special Interest

Adverse events of special interest are pneumonitis/interstitial lung disease (ILD), rash, and infusion-related-reaction and venous thromboembolic (VTE). The MedDRA preferred terms associated with each of these categories are identified in Appendix 7. Additional information will be collected for these events.

Treatment-emergent adverse events of special interest will be included for analysis. Incidence (%) for the following AEs will be provided for each AE of special interest:

- TEAEs by PT
- TEAEs by toxicity grade
- Serious TEAEs by PT
- TEAEs by relationship to study drug
- TEAEs leading to study drug discontinuation by PT.

The above analyses will be repeated for related TEAEs of special interest if appropriate.

Listings of participants with serious AEs and with study drug discontinuation will be provided.

5.6.2.3. Deaths

5.6.2.3.1. Death Due to TEAEs

The number of participants who died due to TEAEs will be summarized by preferred term 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.

5.6.2.3.2. All Deaths

A summary of all death 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.

The similar summaries will be presented for participants who died within 30 days of last study drug dose.

5.6.3. Additional Safety Assessments

5.6.3.1. Clinical Laboratory Tests

Clinical laboratory tests will be displayed for the participants included in the safety analysis set.

Descriptive statistics will be presented for all chemistry and hematology laboratory tests at scheduled time points. Change from baseline over time will be presented. NCI-CTCAE version 5.0 will be used to derive toxicity grades for clinical laboratory tests when applicable. Shift tables from baseline to worst value on treatment (from study treatment start to 30 days after last dose or until the start of subsequent anticancer therapy, whichever is later) will be provided. The worst toxicity grade during the treatment will be tabulated.

An eDISH plot of peak ALT/ AST versus peak BILI will be provided along with a listing of participants who had ALT/ AST values > 3xULN or BILI values > 2xULN.

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

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

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

All potential Hy’s Law cases based on the laboratory criteria will be presented.

5.6.3.2. Vital Signs and Physical Examination Findings

Descriptive statistics will be presented at each scheduled timepoint. The percentage of participants with vital signs values beyond clinically important limits will be presented.

5.6.3.3. Electrocardiogram

A listing of subjects with abnormal ECG readings will be generated.

5.7. Other Analyses

5.7.1. Pharmacokinetics

Not Applicable.

5.7.2. Immunogenicity

Not Applicable.

5.7.3. Pharmacodynamics

Not Applicable.

5.7.4. Pharmacokinetic/Pharmacodynamic Relationships

Not Applicable.

5.7.5. Biomarkers

Not Applicable.

5.7.6. Health Economics

Not Applicable.

5.8. Interim Analyses

There are up-to two interim analyses planned for each cohort: one after stage one to assess if the cohort will continue to stage 2; the other after stage 2 to determine if the cohort will be expanded and the sample size for expansion. Each interim analysis will take place after the last participant to be included finishing his/her Cycle 1 Day 1 measurements. Incidences of IRRs on Cycle 1 Day 1 will be assessed and if 4 or more of these 6 patients experience IRRs, enrollment to the cohort will be stopped. If a cohort at interim 2 experienced 9 or more IRRs out of total 16 patients, this cohort will not be expanded.

5.8.1. Study Evaluation Team

A Study Evaluation Team (SET) will be commissioned to make recommendations with regard to the study conduct after stage 1 and stage 2.

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 List of Abbreviations

AE	adverse event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
AUC	Area under curve
CBR	Clinical benefit rate
CI	confidence interval
CR	Complete response
CRF	case report form
CSR	Clinical Study Report
ECG	Electrocardiogram
eCRF	electronic case report form
IRC	Independent Review Committee
IRR	Infusion Related Reactions
IV	Intravenous
NSCLC	Non-small cell lung cancer
ORR	Overall response rate
OS	Overall survival
PD	Pharmacodynamic
PFS	Progression free survival
PK	pharmacokinetic(s)
PR	Partial response
PT	Preferred term
SAP	Statistical analysis plan
SET	Study evaluation team
SOC	System organ class
TEAE	Treatment-emergent adverse event
WBC	White blood cell

6.2. Appendix 2 Changes to Protocol-Planned Analyses

NA

6.3. Appendix 3 Demographics and Baseline Characteristics

Table below presents a list of the demographic variables that will be summarized.

Continuous Variables	**Summary Type**
Age (years)	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum].
Weight (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.
Sex (male, female, undifferentiated)	
Weight (<80 kg, ≥80 kg)	
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.

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 for advanced/metastatic disease.	
Number of prior lines of systemic therapy for advanced/metastatic disease	
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 (yes, no)	
NSCLC subtype at initial diagnosis (adenocarcinoma, large cell carcinoma, squamous cell carcinoma, other)	
Histology grade at initial diagnosis (moderately differentiated, poorly differentiated, well differentiated, other)	
Cancer stage at initial diagnosis (IA, IB, IIA, IIB, IIIA, IIIB, IIIC, IVA, IVB)	
NSCLC subtype at screening (adenocarcinoma, large cell carcinoma, squamous cell carcinoma, other)	
Histology grade at screening (moderately differentiated, poorly differentiated, well differentiated, other)	
Cancer stage at screening (IIIA, IIIB, IIIC, IVA, IVB)	
Location of metastasis at screening (bone, liver, brain, lymph node, adrenal gland, lung, other)	
Prior systemic therapy (adjuvant, neo-adjuvant, concurrent chemoradiation) taken from early stage	

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

Entered 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 cohort information, participant ID, type of deviation, and reason will be provided for prophylaxis treatment set

6.5. Appendix 5 Prior and Concomitant Medications

Prior and Concomitant medications collected in the CRF page will be coded using the World Health Organization Drug Dictionary (WHO-DD) for safety analysis set.

Prior medications will be summarized by ATC level/preferred terms and treatment. The number and percentage of participants who received prior systemic therapy will be summarized. A similar summary will be conducted for subsequent systemic therapies as well.

Summaries of concomitant medications will be presented by ATC level/preferred terms. 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 incidence (%) of pre-infusion and post-infusion medication will be presented by ATC level/preferred terms.

6.6. Appendix 6 Medical History

Medical history collected at screening visit will be summarized by system-organ class and preferred term.

6.7. Appendix 7 Adverse Events of Special Interest

Adverse events of special interest are defined as follows:

AE of Special Interest 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
Pneumonitis/Interstitial Lung Disease	ACUTE INTERSTITIAL PNEUMONITIS INTERSTITIAL LUNG DISEASE PNEUMONITIS
Venous Thromboembolic (VTE)	THROMBOSIS EMBOLISM Preferred terms from SMQ= Embolic and thrombotic events, venous

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'.

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 treatment indicated*	Clinical signs and symptoms are not taken into consideration for grading.
Leukocytosis	-	-	>100,000/mm3; >100 x 10e9 /L	*Clinical manifestations of leucostasis; urgent treatment 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; *treatment 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; *treatment 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 treatment 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; treatment 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