NOVARTIS

Clinical Development

INC280 (capmatinib), PDR001 (spartalizumab)

CINC280J12201 / NCT04323436

A double-blind, placebo controlled, randomized, phase II study evaluating the efficacy and safety of capmatinib (INC280) and spartalizumab (PDR001) combination therapy versus capmatinib and placebo as first line treatment for locally advanced or metastatic non-small cell lung cancer patients with MET exon 14 skipping mutations

Statistical Analysis Plan (SAP) – Run-in Part 1

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13-Dec-2021	Prior to DB lock	Protocol Amendment v01	• Updated that spartalizumab treatment had been discontinued and Part 2 will not be initiated	Section 1.1 Study design
			• Updated study endpoints and the primary estimand; removed the secondary estimand	Section 1.2 Study objectives and endpoints/Estimand
			[redacted]	Section 2.1.1.7 Window for multiple assessments
			• Removed subgroup analysis	Section 2.2.3 Subgroup of interest
			• Added dose re-escalation of capmatinib	Section 2.4.2 Dose reductions, interruptions and permanent discontinuations
			• Updated time intervals	Section 2.4.1 Study treatment / compliance
			• Updated the analysis for post treatment to listing	Section 2.4.4 Post treatment anti-neoplastic therapy
			• Removed the hypothesis testing for the primary endpoint and updated the primary analysis for the primary estimand.	Section 2.5 Analysis of the primary objective
			• [redacted]	Section 2.7.1 Secondary endpoints
			• Removed two summary tables for AE and updated AESI	Section 2.8.1 Adverse events (AEs)
			[redacted]	[redacted]
			[redacted]	
			[redacted]	[redacted]

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List of abbreviations

[redacted]	[redacted]
AE	Adverse event
AESI	Adverse Events of Special Interest
ALT	Alanine aminotransferase
ALP	Alkaline phosphatase
AST	Aspartate transaminase
ATC	Anatomical Therapeutic Classification
AUC	Area Under the Curve
bid	bis in diem/twice a day
BIRC	Blind Independent Review Committee
BOR	Best Overall Response
CI	Confidence Interval
CR	Complete response
CSR	Clinical Study report
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease Control Rate
DI	Dose Intensity
DOIR	Duration of Intracranial Response
[redacted]	[redacted]
FAS	Full Analysis Set
eCRF	Electronic Case Report Form
[redacted]	[redacted]
IB	Investigator Brochure
LLOQ	Lower Limit of Quantification
MedDRA	Medical Dictionary for Drug Regulatory Affairs
NCI	National Cancer Institute
NSCLC	Non-Small Cell Lung Cancer
OIRR	Overall Intracranial Response
ORR	Overall Response Rate
[redacted]	[redacted]
PD	Progressive disease
PD	Protocol deviations
PDI	Planned Dose Intensity
PDS	Programming and data specification
PFS	Progression-Free Survival
PK	Pharmacokinetics
PR	Partial response
[redacted]	[redacted]
PT	Preferred Terms
[redacted]	[redacted]

[redacted]	[redacted]
RDI	Relative Dose Intensity
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable disease
SOC	System Organ Class
SS	Safety Set
TBL	Total Bilirubin
TFLs	Tables, Figures, Listings
TTIR	Time to Intracranial Response
[redacted]	[redacted]
ULN	Upper Limit of Normality
WHO	World Health Organization

1 Introduction

This Statistical Analysis Plan (SAP) provides detailed statistical methodology for the analysis of data from the open label run-in (Part 1) of study INC280J12201 that will be presented in the final Clinical Study Report (CSR).

The output shells (in-text and post-text) accompanying this document can be found in the Tables, Figures and Listings (TFL) shells document. The specifications for derived variable and datasets can be found in the Programming Datasets Specifications (PDS) document. This version of the SAP is based on the Protocol version 01 released on 13-Oct-2021. All decisions regarding analysis, as defined in the SAP document, have been made prior to database lock of the Part 1 study data.

All changes to the planned analysis described in this document required before or after database lock will be made through an amendment or addendum, respectively. Note that obvious corrections will be made at the time of analysis to address minor formatting or spelling mistakes present in the TFL shells document without the need to amend.

The SAP, TFL shells and PDS documents may also serve as a reference for the creation of any outputs required outside of the CSR, e.g., IB updates, abstracts, posters, presentations, manuscripts and management updates. Data used for these analyses will have a status aligned to the database lock guidance.

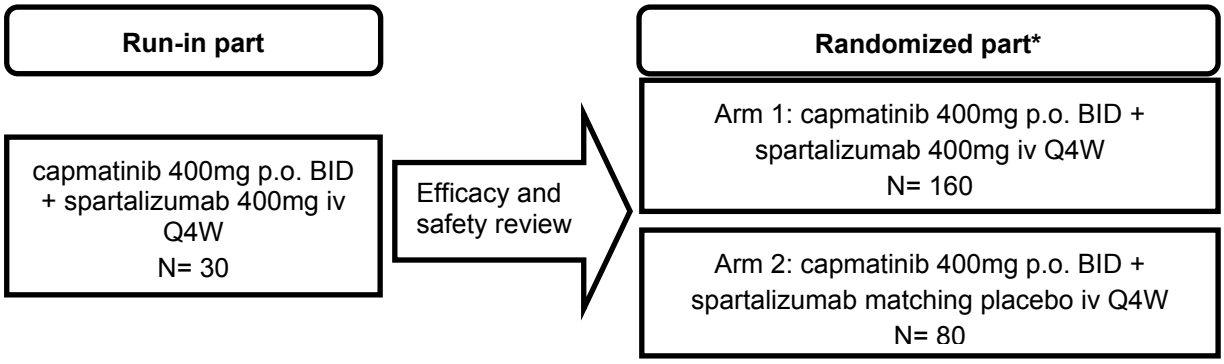
1.1 Study design

This is a two-part, multicenter, phase II study to evaluate the efficacy and safety of capmatinib in combination with spartalizumab in treatment of naive patients with EGFR wt, ALK rearrangement negative advanced NSCLC, harboring MET exon 14 skipping (MET Δex14) mutations.

The study consists of a single arm open label run-in part (Part 1) followed by a double-blind, placebo controlled, randomized part (Part 2). Following the study enrollment halt in Part 1, spartalizumab treatment has been discontinued and the randomized part (Part 2) will not be initiated.

An overview of the study design is provided in Figure 1-1.

Figure 1-1 Study design



*Following the study enrollment halt in Part 1, spartalizumab treatment has been discontinued and the randomized part will not be initiated.

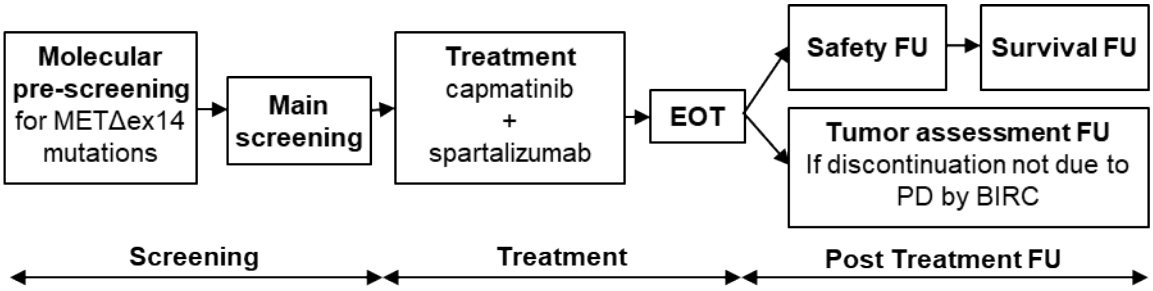
Part 1: Single Arm Run-in Part

Approximately 30 subjects will be treated with the capmatinib and spartalizumab combination during the run-in part of the study (Part 1). The primary objective of Part 1 is to assess the ORR by investigator assessment as per RECIST 1.1 of the combination of capmatinib with spartalizumab.

Refer to Figure 1-2 for an overview on the study design of Part 1.

Figure 1-2 Study design for Part 1

Following the approval of protocol amendment 01, tumor assessment FU and survival FU will not be performed.



EOT: end of treatment; FU: follow-up

1.2 Study objectives and endpoints / Estimands

Objectives and related endpoints for Part 1 are described in Table 1-1 below.

Table 1-1 Study objectives

Objectives	Endpoints
Primary Objectives	**Endpoints for primary objectives**
To evaluate the anti-tumor activity of capmatinib in combination with spartalizumab	Overall Response Rate (ORR) by investigator assessment as per RECIST 1.1
Secondary Objectives	**Endpoints for other secondary objectives**
• To assess safety and tolerability of capmatinib in combination with spartalizumab	• Safety: incidence and severity of AEs and SAEs, changes in laboratory values, vital signs and ECGs. Any clinically significant lab, vital signs, ECG abnormalities will be captured as an AE • Tolerability: dose interruptions, reductions, and dose intensity
• To further evaluate the anti-tumor activity of capmatinib in combination with spartalizumab	• Disease Control Rate (DCR) and PFS by investigator assessment as per RECIST 1.1
• To evaluate the PK of capmatinib and spartalizumab	• Concentrations and derived PK parameters of capmatinib and spartalizumab
[redacted]	

1.2.1 Primary estimand

The primary scientific interest is to estimate the effect of capmatinib in combination with spartalizumab in terms of overall radiological response by investigator assessment as per RECIST 1.1 in first line NSCLC with METΔex14 mutation.

The primary estimand is characterized by the following attributes:

1. Population: adult patients with NSCLC with METΔex14 mutation in first line setting. Further details on the population are provided in Section 5 of protocol amendment 01.
2. Treatment: capmatinib in combination with spartalizumab without any new anti-neoplastic therapy. Further detail about the treatment is provided in Section 6 of protocol amendment 01.
3. Variable: Best Overall Response (BOR) defined as the best response recorded from the start of the treatment until disease progression/recurrence by investigator assessment as per RECIST 1.1
4. Intercurrent events:
   - Discontinuation of spartalizumab for any reason (treatment policy strategy)
   - Discontinuation of tumor assessment follow up with approval of protocol amendment 01 (while on treatment strategy)
   - Any public health emergency as declared by local or regional authorities, e.g., pandemic, epidemic or natural disaster (treatment policy strategy)
   - New anti-neoplastic therapy (while on treatment strategy)

Details on how to handle the intercurrent events are provided in Section 2.5.3.

5. Summary measure: Proportion of subjects with a confirmed CR/PR as BOR, with its corresponding two-sided exact binomial 95% CI.

2 Statistical methods

2.1 Data analysis general information

Study data will be analyzed by Novartis personnel using the most updated SAS® version in the GPS environment. For analyses using R and/or JAGS (e.g., Bayesian analysis) in the DaVinci environment will be used. PK parameters will be calculated using non-compartmental methods available in the most updated version of Phoenix WinNonlin.

Data from all participating centers in this protocol will be combined by part, so that an adequate number of subjects will be available for analysis. Data will be summarized using descriptive statistics (continuous data) and/or contingency tables (categorical data) for demographic and baseline characteristics, efficacy, safety, pharmacokinetic and pharmacodynamics measurements.

Study data in Part 1 will be reported in the final clinical study report (CSR) based on all subjects' data up to the time of completion of the study. There will be no additional CSR. The final CSR will include all outputs planned within the TFL shells document.

The part 1 of this study has one treatment arm: capmatinib + spartalizumab

Qualitative data (e.g., gender, race, etc.) will be summarized by means of contingency tables; a missing category will be included as applicable. Percentages will be calculated using the number of patients in the relevant population or subgroup as the denominator.

Quantitative data (e.g., age, body weight, etc.) will be summarized by appropriate descriptive statistics (i.e., mean, standard deviation, median, minimum, and maximum).

Screen failure patients are those who signed the informed consent, but never started the study treatment for any reason. For these patients, the eCRF data collected will not be included in analyses but will be reported in the CSR as separate listings.

2.1.1 General definitions

2.1.1.1 Investigational drug and study treatment

Investigational drug will refer to capmatinib or spartalizumab. The terms investigational drug and study drug are used interchangeably.

Study treatment will refer to capmatinib + spartalizumab.

2.1.1.2 Date of first/last administration of study treatment

The date of first (last) administration of study treatment is derived as the start (end) date when a non-zero dose of either capmatinib or spartalizumab was administered and recorded on the study treatment eCRF.

2.1.1.3 Study day

The study day describes the day of the event or assessment date, relative to the reference start date. The study day is defined as:

- The date of the event (visit date, onset date of an event, assessment date etc.) − reference start date + 1 if event is on or after the reference start date.
- The date of the event (visit date, onset date of an event, assessment date etc.) − reference start date if event precedes the reference start date.

The reference date for all assessments (safety, efficacy, PK, etc) is the start of study treatment.

The study day will be displayed in the data listings. If an event starts before the reference start date, the study day displayed on the listing will be negative.

2.1.1.4 Time unit

A year length is defined as 365.25 days. A month length is 30.4375 days (365.25/12). If duration is reported in months, duration in days will be divided by 30.4375. If duration is reported in years, duration in days will be divided by 365.25.

2.1.1.5 Baseline

Baseline is the result of an investigation describing the “true” state of the subject before start of study treatment.

For all assessments (safety, efficacy, PK, etc), the last available assessment on or before the date of start of study treatment is taken as “baseline” assessment. In case time of assessment and time of treatment start is captured (e.g., pre-dose ECG), the last available assessment before the treatment start date/time is used for baseline.

For safety parameters (e.g., ECGs or vital signs), where study requires multiple replicates per time point, the average of these measurements would be calculated for baseline (if not already available in the database).

In rare cases where multiple measurements meet the baseline definition, with no further flag or label that can identify the chronological order, then the following rule should be applied: If multiple values are from the same laboratory or collected for ECGs or vital signs, then the last value should be considered as baseline.

If subjects have no value as defined above, the baseline result will be missing.

Laboratory data

If labs with duplicate laboratory measurements taken at the last assessment date on or before the start date of study treatment, then the rule described below will be applied for the calculation of baseline:

1. For lab parameters with CTC grade, the lower CTCAE grade will be considered as the baseline value. For lab parameter with a bi-directional CTC grade, two baselines should be created; with the record with grade below 0 should be the baseline of the 'Hypo' parameter, and the other record should be the baseline for the 'Hyper' parameters.

2. For non-gradable labs:

- If both within normal range: take average value
- If one within normal range and the other outside: take the one within normal range
- If both outside normal range: take the one closest to the normal range

ECGs

Baseline for ECG measurement is the average of the pre-dose replicate measurements on the baseline day. Unscheduled assessments will not be included in the calculation of the average. Study day 1 scheduled pre-dose ECGs will be considered to have been obtained prior to study drug administration if dosing time or ECG time is missing.

If a scheduled pre-dose measurement actually occurred post-dose, then the corresponding measurement will be treated and analyzed similar to an unscheduled post-dose measurement. For unscheduled assessments on study day 1, the assessment is classified as post-baseline.

If subject have no value as defined above, the baseline result will be missing.

2.1.1.6 On-treatment assessment/event and observation periods

For all safety analyses, the overall observation period will be divided into three mutually exclusive segments:

- ***pre-treatment period***: from day of patient's informed consent to the day before first administration of study treatment
- ***on-treatment period***: from date of first administration of study treatment to 30 days after date of last actual administration of any study treatment (including start and stop date)
- ***post-treatment period***: starting at day 31 after date of last administration of study treatment

If dates are incomplete in a way that clear assignment to pre-, on-, post-treatment period cannot be made, then the respective data will be assigned to the on-treatment period.

Safety summaries will primarily include only data from the on-treatment period. Select summaries of related adverse events and death will be produced for the combined on-treatment and post-treatment periods of study treatment (see Section 2.8.1 and Section 2.8.2).

2.1.1.7 Last contact date

The last contact date will be derived for patients not known to have died at the analysis cut-off using the last complete date among the following:

Table 2-1 Last contact date data sources

Source data	Conditions
Last contact date/last date patient was known to be alive from Survival eCRF page	Patient status is reported to be alive or unknown in the survival eCRF page
Start/End dates from further antineoplastic therapy	Non-missing medication/procedure term.
Start/End* dates from study treatment eCRF	Non-missing dose. Doses of 0 are allowed.

Source data	Conditions
End of treatment date from end of treatment page	No condition.
Tumor (RECIST) assessment date	Evaluation with a response.
Date of verification for treatment beyond RECIST 1.1 PD	Will the subject continue treatment beyond disease progression as per RECIST 1.1? marked as 'Yes'
PK collection dates	Was sample taken marked as 'Yes'.
Vital signs/ECGs/Laboratory date	At least one non-missing parameter value
Performance Status date	Non-missing performance status
Start/End dates of AE	Non-missing verbatim term

The last contact date is defined as the latest complete date from the above list on or before the data cut-off date. The cut-off date will not be used for last contact date unless the patient was seen or contacted on that date. No date post cut-off date will be used. Completely imputed dates (e.g., the analysis cut-off date programmatically imputed to replace the missing end date of a dose administration record) will not be used to derive the last contact date. Partial date imputation is allowed for event (death)/censoring is coming from 'Survival information' eCRF.

The last contact date will be used for censoring of patients in the analysis of time to event endpoints.

2.2 Analysis sets

Full Analysis Set (FAS)

The Full Analysis Set (FAS) comprises all subjects to whom study treatment has been assigned and who received at least one dose of study treatment (i.e., at least one dose of any component of the study treatment that is capmatinib or spartalizumab (including incomplete infusion)).

Safety Analysis Set (SS)

The FAS and Safety Set are identical.

Capmatinib Pharmacokinetic analysis sets (INC-PAS and INC-FPAS)

The capmatinib PAS includes two sets, the capmatinib pharmacokinetic analysis set (INC-PAS) and capmatinib full pharmacokinetic analysis set (INC-FPAS) which will be used for non-compartmental analysis (NCA).

The INC-PAS includes all subjects who have provided at least one evaluable capmatinib PK concentration. For a capmatinib PK concentration to be evaluable, a subject must:

- Have taken a dose of capmatinib prior to sampling

- For pre-dose samples, do not vomit within 4 hours after the dosing of capmatinib prior to sampling.
- For post-dose samples, do not vomit within 4 hours after the dosing of capmatinib
- For pre-dose sample, have the sample collected before the next dose administration and 9-15 hours after the last dose administration.

The INC-FPAS includes all INC-PAS subjects who have provided a capmatinib evaluable PK profile on cycle 3 day 1 (only applicable to subjects with extensive PK sampling). A capmatinib PK profile is considered evaluable if all of the following conditions are satisfied:

- Subject has received one dose of the planned capmatinib treatment
- Subject has provided at least one valid primary PK parameter
- Subjects did not vomit within 4 hours after the dosing of capmatinib

Spartalizumab Pharmacokinetic analysis sets (PDR-PAS and PDR-FPAS)

The spartalizumab PAS includes two sets, spartalizumab pharmacokinetic analysis set (PDR-PAS) and spartalizumab full pharmacokinetic analysis set (PDR-FPAS).

The PDR-PAS includes all subjects who have provided at least one evaluable PK concentration. For a concentration to be evaluable, a subject must:

- Have received one of the planned doses (complete infusion) of spartalizumab prior to sampling.
- For pre-dose samples, have the sample collected before the next dose administration.

The PDR-FPAS includes all subjects who provide an evaluable PK profile (Note: Only applicable to subjects with extensive PK sampling). A profile is considered evaluable if all of the following conditions are satisfied:

- Subject has received one dose (complete infusion) of the planned spartalizumab treatment
- Subject has provided at least one valid primary PK parameter
- For pre-dose samples, have the sample collected before the next dose administration.

Only PK blood samples with date and time and for which the last prior dose dates and times are adequately recorded will be included in the PK analyses.

Any blood samples with missing collection date or time or missing associated study drug dosing date or time will be excluded. Additionally, a PK sample can be considered not evaluable as per scientific judgment of the clinical pharmacology expert. In such case, the PK sample is excluded from the analyses and the reason for its exclusion will be documented.

2.2.1 Classification of subjects

Subjects may be excluded from the analysis populations defined above based on the protocol deviations (PD) entered in the database and/or on specific classification rules defined in Table 2-2.

Table 2-2 Subject classification based on PDs and non-PD criteria

Analysis set	Protocol deviations leading to exclusion	Non protocol deviation leading to exclusion
Full analysis set	No written inform consent	Subject not receiving a dose of study treatment
Safety set	No written inform consent	Subject not receiving a dose of study treatment
INC-PAS and PDR-PAS	No written informed consent C1D1 Spartalizumab PK [redacted] sample not collected or collected after dosing	Subject not receiving a dose of study treatment Subject not providing any evaluable PK concentration for capmatinib or spartalizumab, respectively
INC-FPAS and PDR-FPAS	No written informed consent C1D1 Spartalizumab PK [redacted] sample not collected or collected after dosing	Subject not receiving a dose of study treatment Subject not providing a valid PK profile for capmatinib or spartalizumab, respectively

2.2.2 Withdrawal of inform consent

Any data collected after a subject withdraws informed consent from all further participation in the study, will not be included in the analysis. Data collected on the same date as withdrawal of informed consent are reported. The date on which a subject withdraws full consent is recorded in the eCRF.

[redacted]

2.2.3 Subgroup of interest

Not applicable

2.3 Patient disposition, demographics and other baseline characteristics

Summaries and listings described in this section will be based on the FAS.

2.3.1 Patient disposition

The number (%) of treated subjects included in the FAS will be presented. The number (%) of screened and not-treated subjects.

The following summaries will be tabulated:

- Number (%) of subjects treated.

- Number (%) of subjects who are still on-treatment at the time of cut-off (to be removed at time of final CSR).
- Number (%) of Subjects who discontinued study treatment and primary reasons for discontinuation.
- Number of (%) Subjects followed up/not followed after discontinuation of study treatment and reasons for post-treatment follow-up discontinuation.

2.3.2 Demographic

Demographic data and other baseline characteristics data (including age, sex, race, ethnicity, height, weight, ECOG performance status, smoking history) will be listed and summarized. In addition, following age categories will be summarized: 18- <65 years, 65- < 85 years, and ≥ 85 years.

2.3.3 Medical history

A listing of medical history and current medical conditions will be provided, using the latest Medical Dictionary for Regulatory Activities (MedDRA) terminology available at the time of reporting.

2.3.4 Diagnosis and extent of cancer

The summary and listing of diagnosis and extent of cancer (disease history) will include: details of tumor histology/cytology, histologic grade, stage at initial diagnosis, stage at time of study entry, types of lesions at baseline, current extent of disease (metastatic sites), and PD-L1 expression at baseline.

Imputation rules for partially missing dates are provided in Section 5.1.3.3.1.

2.3.5 Protocol deviations

The FAS will be used for the protocol deviation summary tables and listing. The number (%) of patients with any CSR-reportable protocol deviation will be tabulated by the deviation category.

2.3.6 Analysis sets

The number (%) of patients in each analysis set (defined in Section 2.2) will be summarized and listed.

2.4 Treatments (study treatment, concomitant therapies, compliance)

2.4.1 Study treatment / compliance

Duration of exposure, actual cumulative dose, dose intensity (DI) and relative dose intensity (RDI) will be summarized separately for each component of study treatment. Duration of exposure will also be calculated for the study treatment.

Duration of exposure will be categorized into time intervals (e.g., <6 weeks, 6 - <12 weeks, 12 - <18 weeks, 18 - <24 weeks, 24 - < weeks, 48 - <72 weeks and >72 weeks); frequency counts and percentages will be presented for the number (%) of subjects in each interval. Continuous summarized for duration of exposure will be provided using weeks as time units.

The number (%) of subjects who have dose adjustment (only reductions will be summarized in the analysis) or interruptions, and the reasons, will be summarized for all subjects. Subject level listings of all doses administered on treatment along with dose change reasons will be produced.

The safety set will be used for all summaries and listings of study treatment.

2.4.1.1 Duration of exposure for investigational drug

Duration of exposure to capmatinib (days) = (last date of exposure to capmatinib) – (date of first administration of capmatinib) + 1.

With:

1. The first date of exposure for capmatinib is the first date when a non-zero capmatinib dose was administered and recorded on the study treatment eCRF.
2. The last date of exposure to capmatinib is the end date from the last dose administration record non-zero capmatinib dose is recorded in the study treatment eCRF.

Duration of exposure to spartalizumab (days) = (last date of exposure to spartalizumab) – (date of first administration of spartalizumab).

With:

1. The first date of exposure for spartalizumab is the first date when a non-zero spartalizumab dose was administered and recorded on the study treatment eCRF.
2. The last date of exposure to spartalizumab is the end date from the last dose administration record non-zero spartalizumab dose is recorded in the study treatment eCRF + 27 days (if no death or no lost to follow-up is observed).
3. The last date of exposure to spartalizumab is the earliest date among last dose administration record non-zero spartalizumab dose + 27 days and date of death if the subject died.
4. The last date of exposure to spartalizumab is the earliest date among last dose administration record non-zero spartalizumab dose + 27 days and date of last contact date if the subject was lost to follow-up.

2.4.1.2 Cumulative dose

Cumulative dose of a study treatment is defined as the total dose given during the study treatment exposure and will be summarized for each of the study treatment components, respectively.

The planned cumulative dose for a study treatment component refers to the total planned dose as per the protocol up to the last date of investigational drug administration. The planned cumulative dose is not summarized/listed. It is used for relative dose intensity calculations.

The actual cumulative dose refers to the total actual dose administered, over the duration for which the subject is on the study treatment as documented in the study treatment eCRF.

For subjects who did not take any drug, the actual cumulative dose is by definition equal to zero for that drug.

For capmatinib (continuous dosing), the actual cumulative dose is the sum of the non-zero doses recorded over the dosing period. The planned cumulative dose is the planned starting dose summed over the same dosing period.

For spartalizumab (intermittent dosing), the actual cumulative dose should be defined based on the days when the subject is assumed to have taken a non-zero dose during dosing periods (number of infusions taken over the treatment period). The planned cumulative dose is the planned starting dose summed over the number of expected infusions during treatment period (e.g, a subject treated for 60 days is expected to have three infusions).

2.4.1.3 Dose intensity and relative dose intensity

For dose intensity calculations, the unit of time for capmatinib will be days and for spartalizumab will be cycles.

For capmatinib, the **dose intensity** (DI) is defined as follows:

DI (mg / days) = Actual Cumulative dose (mg) / Duration of exposure to capmatinib (days).

For example:

The duration of exposure is 56 days and the subject received 50 days of full dosing

DI (mg/day) = 40 000 (mg) / 56 (Day) = 714 (mg/day)

For spartalizumab, the **dose intensity** (DI) is defined as follows:

DI (mg / cycles) = length of cycle * (Actual Cumulative dose (mg) / duration of exposure to spartalizumab (days)).

For example:

The duration of exposure is 56 days and the subject received two complete infusions

DI (mg/cycle) = 28 (days) * (800 (mg) / 56 (days)) = 400 (mg/cycle)

For subjects who did not take any drug the DI is by definition equal to zero.

For capmatinib, the **Planned dose intensity** (PDI) is defined as follows:

PDI (mg / days) = Planned Cumulative dose (mg) / Duration of exposure to capmatinib (days)

For example:

The duration of exposure is 56 days, and the subject is planned to receive 56 days of dosing

PDI (mg/day) = 44 800 (mg) / 56 (Day) = 800 (mg/day)

For spartalizumab, the **Planned dose intensity** (PDI) is defined as follows:

PDI (mg / cycles) = length of cycle * (Planned Cumulative dose (mg) / duration of exposure to spartalizumab (days)).

For example:

The duration of exposure is 56 days, and the subject is planned to receive two infusions

PDI (mg / cycles) = 28 (days) * (800 (mg) / 56 (days)) = 400 (mg/cycle)

Relative dose intensity (RDI) is defined as follows:

RDI = DI (mg / unit of time) / PDI (mg / unit of time)

DI and RDI will be summarized separately for each of the study treatment components, using the duration of exposure of each of the components. RDI will be summarized in percentages. Summary of RDI includes categorical summaries. The RDI categories are < 50%, ≥ 50% - < 75%, ≥ 75% - < 90%, ≥ 90% - < 110% and ≥ 110%.

2.4.2 Dose reductions, interruptions and permanent discontinuations

The number of subjects who have dose reductions, permanent discontinuations or interruptions, and the reasons, will be summarized separately for each of the study treatment components.

The 'Type of change' field from the study treatment CRF pages will be used to determine the dose interruptions. Dose reductions will be derived programmatically using the dosing information as described below.

The corresponding fields 'Reason for change' will be used to summarize the reasons.

A dose change is recorded when 'Dose change' is entered on the 'Type of change' field on the DAR CRF page, where actual dose administered/total daily dose is different from the prescribed dose. In protocol version 01, dose re-escalation of capmatinib after dose reduction will be allowed only once, given no AE leading to dose modification is observed after at least 1 cycle (4 weeks) of study treatment at the reduced dose. The dose re-escalation will be considered as a dose change.For the purpose of summarizing interruptions and reasons, in case multiple entries for interruption that are entered on consecutive days with different reasons will be counted as separate interruptions. However, if the reason is the same in this mentioned multiple entries on consecutive days, then it will be counted as one interruption.

Dose reduction (only for capmatinib**)**: A dose reduction where the prescribed dose level is lower than the previous prescribed dose level or where the actual dose administered/total daily dose is lower than the calculated dose amount based on the prescribed dose. Therefore, any dose change to correct a dosing error will not consider a dose reduction. Only dose change is collected in the CRF, number of reductions will be derived programmatically based on the change and the direction of the change.

Dose interruption: Actual dose administered equal to zero, between the first and last non-zero doses, following a non-zero actual dose administered. Number of dose interruptions and corresponding reason will be summarized.

2.4.3 Study treatment beyond RECIST progression

The number (%) of subjects who continue study treatment beyond RECIST 1.1 progression according to local investigator assessment based on protocol specified criteria will be summarized. It includes all subjects who received any study treatment (i.e., at least one dose of

any component of the study treatment) after RECIST 1.1 progression assessed by local investigator.

2.4.4 Prior, concomitant and post therapies

Summaries and listings described in this section will be based on the FAS.

2.4.4.1 Prior anti-neoplastic therapies

The number (%) of subjects who received any prior anti-neoplastic medication, radiotherapy or surgery will be summarized.

The summary of prior anti-neoplastic medications will include the total number of regimens (note: there can be more than one medication per regimen), therapy type at last treatment, setting at last treatment. Prior antineoplastic medications will also be summarized by Anatomical Therapeutic Chemical (ATC) class, and preferred term.

The summary of prior anti-neoplastic radiotherapy will include the radiotherapy locations, (including all locations recorded for each subject), setting at last radiotherapy, and best response at last radiotherapy.

The summary of prior anti-neoplastic surgery will include the time (in months) between the last surgery (non-biopsy procedure) to start of study treatment, procedure at last surgery and residual disease at last surgery.

All prior anti-neoplastic medication, radiotherapy and surgery will be listed.

Imputation rules for partially missing dates are provided in Section 5.1.3.1.

2.4.4.2 Post treatment anti-neoplastic therapy

Anti-neoplastic therapies (medications, radiotherapies and surgeries) since discontinuation of study treatment will be listed.

2.4.4.3 Concomitant therapies

Concomitant therapy is defined as all interventions (therapeutic treatments and procedures) other than the study treatment administered to a patient coinciding with the study treatment period. Concomitant therapy includes medications (other than study drugs) starting on or after the start date of study treatment or medications starting prior to the start date of study treatment and continuing after the start date of study treatment.

Concomitant medications will be coded using the World Health Organization (WHO) Drug Reference Listing (DRL) dictionary that employs the WHO Anatomical Therapeutic Chemical (ATC) classification system and summarized by lowest ATC class and preferred term using frequency counts and percentages. Surgical and medical procedures will be coded using MedDRA and summarized by SOC and preferred term. Concomitant medications with immunosuppressive intent will be summarized by lowest ATC class and preferred term using frequency counts and percentages. These summaries will include:

1. Medications starting on or after the start of study treatment but no later than 30 days after last dose of study treatment and

2. Medications starting prior to start of study treatment and continuing after the start of study treatment.

Listings will be provided to report medications starting between 30 days after last dose of study treatment and 150 days after last dose of spartalizumab.

2.5 Analysis of the primary objective

The primary objective is to evaluate the anti-tumor activity of capmatinib in combination with spartalizumab, as measured by overall response rate (ORR) by investigator assessment according to RECIST 1.1 (see [Appendix 16.1.1-Protocol-Section 16.1]).

2.5.1 Primary endpoint / estimand

Overall response rate (ORR) is defined as the proportion of subjects with confirmed best overall response (BOR) of complete response (CR) or partial response (PR) according to RECIST 1.1 (see [Appendix 16.1.1-Protocol-Section 16.1]). ORR will be calculated based on the FAS.

Subjects with only non-measurable disease at baseline will be part of the analysis and will be included in the numerator only if a complete response was observed.

2.5.2 Statistical hypothesis, model, and method of analysis

Overall response rate (ORR) by investigator assessment is calculated based on the data from the FAS and the corresponding 95% CI based on the exact binomial distribution (Clopper and Pearson 1934) will be presented.

Participants who had never received one of the investigational drugs will be excluded from the efficacy analysis.

2.5.3 Handling of intercurrent events for the primary estimand

The primary estimand will account for the different intercurrent events as follows:

1. **Discontinuation of spartalizumab for any reason:** BOR will take into account all available tumor assessments irrespective of spartalizumab discontinuation reasons.
2. **Discontinuation of tumor assessment follow up with approval of protocol amendment:** BOR will take into account all available tumor assessments up to the last valid tumor assessment prior to approval of protocol version 01.
3. **Any public health emergency as declared by local or regional authorities, e.g., pandemic, epidemic or natural disaster:** BOR will take into account all tumor assessments irrespective of any public health emergency.
4. **New anti-neoplastic therapy:** Tumor assessment data collected after starting new anti-neoplastic therapy will be excluded from the BOR derivation.

2.5.4 Handling of missing values/censoring/discontinuations

Subjects in the FAS with unknown BOR will be noted as such in the appropriate tables/listings and counted as non-responders in the ORR calculation.

If there is no baseline tumor assessment, all post-baseline overall lesion responses are expected to be 'Unknown'. If no valid post-baseline tumor assessments are available, the best overall response must be "Unknown" unless progression or death is reported.

If any new anti-neoplastic therapy is taken while on study any subsequent assessments will be excluded from the BOR derivation.

Subjects without confirmed CR/PR, due to lack of subsequent tumor assessment after one CR/PR, will be considered as non-responders.

2.5.5 Supportive and supplementary analysis

A sensitivity analysis may be performed where subjects without a valid post-baseline assessment (unless PD or death is reported before that time) are excluded from the calculation of the ORR.

As a supportive analysis, the change in tumor size will be describe using a waterfall plot presenting the best percentage change from baseline in the sum of diameters of all target lesions.

2.6 Analysis of the key secondary objective

Not applicable.

2.7 Analysis of secondary efficacy objective(s)

2.7.1 Secondary endpoints

The secondary efficacy endpoints are disease control rate (DCR) and progression free survival (PFS) by investigator assessment as per RECIST 1.1.

Disease control rate (DCR)

DCR is defined as the proportion of subjects with a confirmed best overall response (BOR) of complete response (CR), partial response (PR), stable disease (SD), and non-CR/non-PD (for subjects without target lesions) according to RECIST 1.1 (see [Appendix 16.1.1-Protocol-Section 16.1]).

DCR is calculated based on the data from the FAS and the corresponding 95% CI based on the exact binomial distribution (Clopper and Pearson 1934) will be presented.

Participants who had never received one of the investigational drugs will be excluded from the DCR analysis.

Progression free survival (PFS)

PFS is defined as the time from the date of start of treatment to the date of the first documented progression according to RECIST 1.1, or death due to any cause. Clinical deterioration without objective radiological evidence will not be considered as documented disease progression.

PFS will be summarized using the KM method, based on FAS. Median PFS, with corresponding 95% CI, and 25th and 75th percentiles (Brookmeyer and Crowley 1982, Klein and Moeschberger 1997) will be presented. KM estimates for PFS proportions at specific timepoints (3, 6, 9, 12, and 18

months), along with 95% CI (Greenwood's formula, Kalbfleisch and Prentice 2002) will also be provided. The number (%) of events and subjects censored will also be summarized.

Participants who had never received one of the investigational drugs will be excluded from the PFS analysis.

PFS will be censored at the date of the last adequate tumor assessment prior to the earliest of analysis cut-off date, the start of a subsequent anti-neoplastic therapy (if any), if the event occurred after two or more missing tumor assessments, or study treatment discontinuation before radiological progression or death (for patients who discontinued study treatment before radiological progression/death and also prior to the approval of protocol version 01, PFS will be censored at the date of the last adequate tumor assessment prior to the approval of protocol version 01). The date of last adequate tumor assessment is the date of the last tumor assessment with overall lesion response of CR, PR or SD before an event or a censoring reason occurred. If no post-baseline assessments are available (before an event or a censoring reason occurred), the date of enrollment will be used. If a subject has no progression or death, the subject is censored at the date of last adequate tumor assessment.

The number of subjects censored and reasons for censoring will be summarized using descriptive statistics.

2.8 Safety analyses

The Safety set will be used for summaries and listings of safety data.

The overall observation period will be divided into 3 mutually exclusive segments:

Pre-treatment period:

- from day of subject's first informed consent to the day before first administration of study treatment

On-treatment period:

- from date of first administration of study drug to 30 days after the last actual administration of study treatment (including start and stop date)

Post-treatment period:

- Starting at date 31 after the last administration of study treatment

2.8.1 Adverse events (AEs)

Adverse event (AE) summaries will include all AEs occurring during on-treatment period. All AEs collected in the AE eCRF page will be listed along with the information collected on those AEs e.g., AE relationship to study drug, AE outcome etc. AEs starting during the post-treatment period will be flagged in the listings.

Adverse events (AEs) will be summarized by number and percentage of subjects having at least one AE, having at least one AE in each primary system organ class (SOC) and for each preferred term (PT) using MedDRA coding. A subject with multiple occurrences of an AE will be counted only once in the respective AE category. A subject with multiple CTCAE grades for the same preferred term will be summarized under the maximum CTCAE grade recorded for the event.

AE with missing CTCAE grade will be included in the 'All grades' column of the summary tables.

In AE summaries by primary SOC and PT, the primary SOC will be presented alphabetically and the PT will be sorted within primary SOC in descending frequency. Table by either primary SOC or PT will be sorted in descending frequency.

The following adverse event summaries will be produced for all subjects:

- Overview of adverse events summarized by relationship and deaths (number and % of subjects who died, with any AE, any SAE, fatal SAEs, AEs leading to dose reduction/interruptions, AE leading to treatment discontinuation)
- AEs by SOC and PT, summarized by relationship (all AEs and AEs related to study treatment).
- SAEs summarized by relationship (all SAEs and SAEs related to study treatment) and severity.
- AEs leading to study treatment discontinuation (all AEs and AEs related to study treatment).
- AEs leading to study treatment dose reduction/interruption.

The following listings will be produced:

- All adverse events (safety set)
- All serious adverse events (safety set) (including those from the pre and post-treatment periods)
- Adverse events among subjects who were not treated (screening failure subjects)

EudraCT and clinicaltrials.gov requirements for AEs and Deaths summaries

For the legal requirements of clinicaltrials.gov and EudraCT, two required tables on on-treatment adverse events which are not serious adverse events with an incidence greater than 5% and on on-treatment SAEs and SAEs suspected to be related to study treatment will be provided by SOC and PT on the safety set population.

If for the same subject, several consecutive AEs (irrespective of study treatment causality, seriousness and severity) occurred with the same SOC and PT:

- a single occurrence will be counted if there is ≤ 1 day gap between the end date of the preceding AE and the start date of the consecutive AE
- more than one occurrence will be counted if there is > 1 day gap between the end date of the preceding AE and the start date of the consecutive AE

For occurrence, the presence of at least one SAE / SAE suspected to be related to study treatment / non-SAE has to be checked in a block e.g., among AEs in a ≤ 1 day gap block, if at least one SAE is occurring, then one occurrence is calculated for that SAE.

The number of deaths resulting from SAEs suspected to be related to study treatment and SAEs irrespective of study treatment relationship will be provided by SOC and PT.

2.8.1.1 Adverse events of special interest / grouping of AEs

An adverse event of special interest (AESI) is a grouping of adverse events that are of scientific and medical concern specific to spartalizumab and/or capmatinib. These groupings are defined using MedDRA terms, SMQs (standardized MedDRA queries), HGLTs (high level group terms), HLT (high level terms) and PTs (preferred terms). Customized SMQs (Novartis MedDRA queries, NMQ) may also be used. A NMQ is a customized group of search terms which defines a medical concept for which there is no official SMQ available or the available SMQ does not completely fit the need. It may include a combination of single terms and/or an existing SMQ, narrow or broad.

For each specified AESI for each study drug, the number and percentage of subjects with at least one event of the AESI occurring during on-treatment period will be summarized for each study drug separately:

- Overview of adverse events of special interest for capmatinib
- Overview of adverse events of special interest for spartalizumab

A listing of all grouping levels down to the MedDRA preferred terms used to define each AESI will be generated.

Note: From the eCRS, only risk where “Core Safety Risk” = Y should be selected to report Adverse events of special interest in the CSR (the variable name in GPS, for “Core Safety Risk”, is SP).

2.8.2 Deaths

Separate summaries for on-treatment deaths and all deaths (including post-treatment deaths) will be produced for all subjects by SOC and PT.

All deaths will be listed for the safety set, post treatment deaths will be flagged. A separate listing of deaths will be provided for screening failure subjects.

2.8.3 Laboratory data

The summaries will include all assessments (including unplanned assessment) available for the lab parameter collected no later than 30 days after the last study treatment administration date (see Section 2.1.1.6). Details on derivations are provided in Section 5.3.

The following summaries will be produced for hematology and biochemistry laboratory data (by laboratory parameter and treatment):

- Shift tables using CTC grades to compare baseline to the worst on-treatment value.
- For laboratory tests where CTC grades are not defined, shift tables using the low/normal/high/(low and high) classification to compare baseline to the worst on-treatment value.

The following listings will be produced for the laboratory data:

- Listing of all CTC grade 3 or 4 laboratory toxicities

Liver function parameters

Liver function parameters of interest are total bilirubin (TBL), ALT, AST and alkaline phosphatase (ALP).

The number (%) of subjects with newly occurring or worsening values will be summarized:

- ALT or AST > 3xULN
- ALT or AST > 5xULN
- ALT or AST > 8xULN
- ALT or AST > 10xULN
- ALT or AST > 20xULN
- TBL > 2xULN
- TBL > 3xULN
- For subjects with AST and ALT ≤ ULN at baseline
  - ALT or AST >3x ULN & TBL >2x ULN
  - ALT or AST >3x ULN & TBL >2x ULN & ALP >=2x ULN
  - ALT or AST >3x ULN & BILI >2x ULN & ALP <2x ULN
- For subjects with AST and ALT > ULN at baseline (Bsl)
  - Elevated ALT or AST (*) & BILI (>2x Bsl and 2x ULN)
  - Elevated ALT or AST (*) & BILI (>2x Bsl and 2x ULN) & ALP ≥2x ULN
  - Elevated ALT or AST (*) & BILI (>2x Bsl and 2x ULN) & ALP <2x ULN

* Elevated AST or ALT defined as: >3x ULN if ≤ ULN at baseline, or (>3x Bsl or 8x ULN) if > ULN at baseline

2.8.4 Other safety data

2.8.4.1 ECG data

12-lead ECGs including PR, QRS, QT, QTcF intervals, and HR will be obtained for each subject during the study. ECG data will be read and interpreted locally. The average of the ECG parameters at each assessment should be used in the analyses.

The number and percentage of subjects with notable ECG values will be presented.

- QT, or QTcF
  - New value of > 450 and ≤ 480 ms
  - New value of > 480 and ≤ 500 ms
  - New value of > 500 ms
  - Increase from baseline of > 30 ms to ≤ 60 ms
  - Increase from baseline of > 60 ms
- HR
  - Increase from baseline >25% and to a value > 100 bpm
  - Decrease from baseline >25% and to a value < 50 bpm

- PR
  - Increase from baseline >25% and to a value > 200 ms
  - New value of > 200 ms
- QRS
  - Increase from baseline >25% and to a value > 120 ms
  - New values of QRS > 120 ms

ECGs collected during on-treatment will be summarized. The number and percentage of subjects with notable ECG values will be presented for the safety set. A listing of subjects with notable ECGs will be provided and value measure during the post-treatment follow up will be flagged in the listing.

2.8.4.2 Vital signs

Vital sign assessments are performed to characterize basic body function. The following parameters were collected: height (cm), weight (kg), body temperature (°C), heart rate (beats per minute), systolic and diastolic blood pressure (mmHg).

Vital signs collected during on-treatment will be summarized. Values measured during the post-treatment period will be flagged in the listings. The number and percentage of subjects with notable vital sign values (high/low) will be presented. A listing of subjects with notable vital signs will be provided and value measure during the post-treatment follow up will be flagged in the listing.

Table 2-3 Criteria for notable vital sign values

Vital sign (unit)	Notable high value	Notable low value
Weight (kg)	increase > 10% from Baseline	decrease > 10% from Baseline
Systolic blood pressure (mmHg)	>=180 with increase from baseline of ≥20	<=90 with decrease from baseline of >=20
Diastolic blood pressure (mmHg)	>=105 with increase from baseline of >=15	<=50 with decrease from baseline of >=15
Pulse rate (bpm)	>=100 with increase from baseline of >25%	<=50 with decrease from baseline of > 25%
Body temperature (°C)	>= 39.1°C	-

2.9 Pharmacokinetic endpoints

All PK concentration analyses and PK concentration summary statistics will be based on the INC-PAS and PDR-PAS. PK parameters summary statistics will be based on the INC-FPAS and PDR-FPAS.

PK parameters

Pharmacokinetic parameters will be determined by non-compartmental method(s) using the pharmacokinetic profile of capmatinib and spartalizumab. PK parameters listed in Table 2-4 will be derived and reported, when feasible.

Table 2-4 Non-compartmental pharmacokinetic parameters for capmatinib and spartalizumab

AUClast	The AUC from time zero to the last measurable concentration sampling time (tlast) (ng x hr x mL-1 for capmatinib; μg x day x mL-1 for spartalizumab)
AUCtau	The AUC calculated to the end of a dosing interval (tau) at steady-state (ng x hr x mL-1 for capmatinib; μg x day x mL-1 for spartalizumab)
Cmax	The maximum (peak) observed plasma, blood, serum, or other body fluid drug concentration after single dose administration (ng/mL for capmatinib; μg/mL for spartalizumab)
Tmax	The time to reach maximum (peak) plasma, blood, serum, or other body fluid drug concentration after single dose administration (hr for capmatinib; day for PDR)

Descriptive statistics will be presented for all pharmacokinetic parameters, as described below.

Table 2-5 Descriptive analysis

Parameters	Descriptive statistics
AUC[(1)], C_{max},	Mean standard deviation, CV% mean, geometric mean, CV% geo-mean, median, minimum, and maximum. 90% CI for $R_{acc.}$
T_{max}	Median, minimum, and maximum.
[(1)] Includes, AUC_{tau}, AUC_{last} (or all AUC parameters) CV% = coefficient of variation (%) = sd/mean*100 CV% geo-mean = sqrt (exp (variance for log transformed data)-1) *100	

Missing PK parameter values will not be imputed. A listing of derived PK parameters per subject will be produced.

Concentrations

PK concentration data for each compound will be listed for all subjects by visit/sampling time point. Descriptive summary statistics will be provided by visit/sampling time point for all subjects, including the frequency (n, %) of concentrations below the lower limit of quantification (LLOQ) and reported as non-zero.

Summary statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum and maximum.

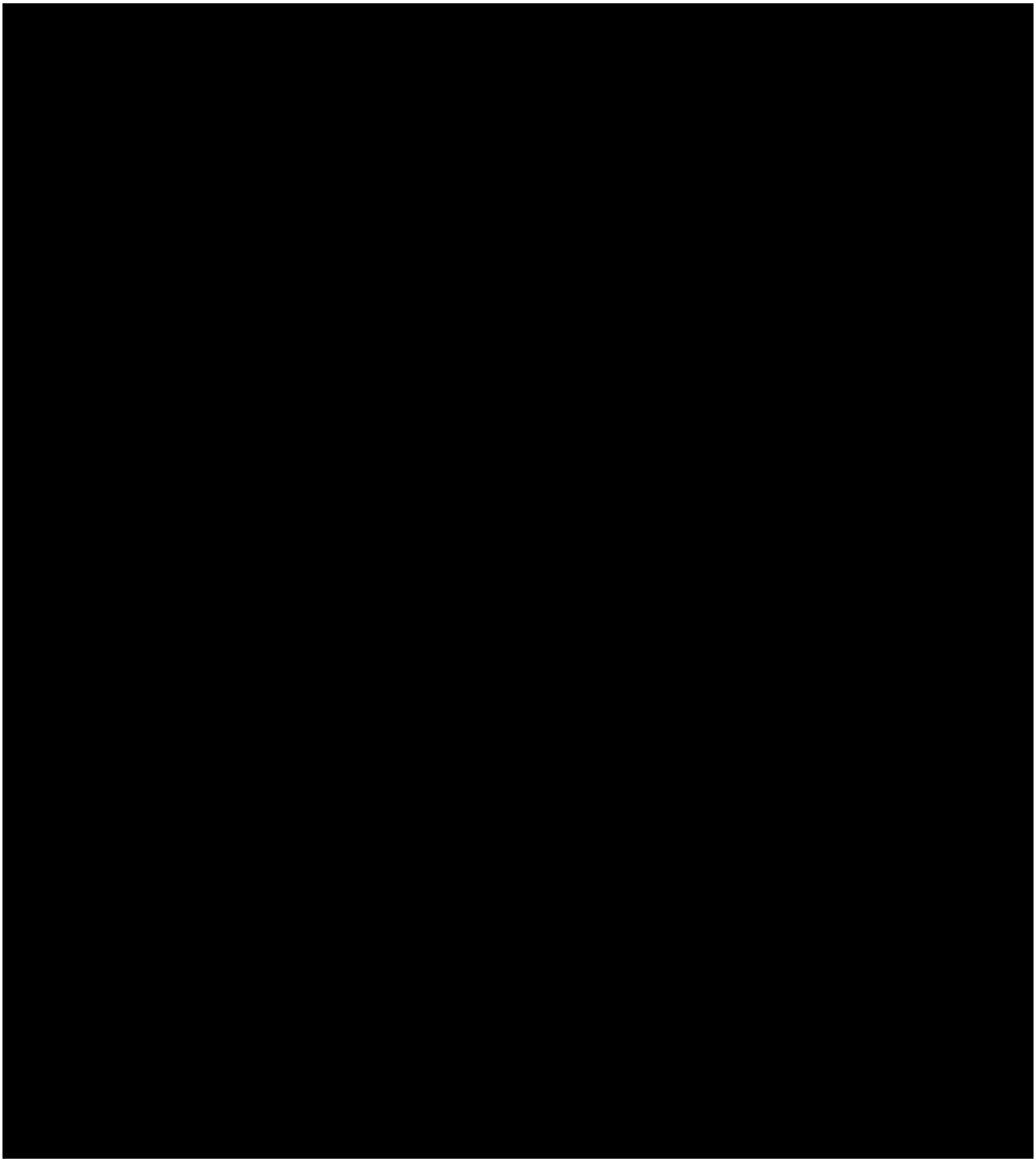
Descriptive graphical plots of individual concentration versus time profiles and mean concentration versus time profiles will be generated.

2.9.1 Data handling principles

All concentrations below the lower limit of quantitation (LLOQ) or missing data will be labeled as such in the concentration data listings. Concentrations below the LLOQ will be treated as zero in summary statistics and for the calculation of pharmacokinetic parameters, unless otherwise stated under the Pharmacokinetic Analysis Set. Concentrations below LLOQ will be treated as zero in summary statistics and for PK parameter calculations. Zero concentrations will not be included in the geometric mean and geometric CV% calculations.

Missing values for any PK data will not be imputed and will be treated as missing.

At the time of analysis, concentration data from subjects may be removed from the estimation of certain PK parameters depending on the number of available blood samples, concomitant medications, vomiting, etc. Specific time points might be removed from the analysis set if technical issues with the sample are reported (e.g., sampling issues, missing information). These subjects and concentration data points will be identified at the time of analysis.



2.14 Interim analysis

No formal interim analysis is planned.

3 Sample size calculation

No formal statistical power calculations to determine sample size were performed for this part of the study.

Approximately 30 subjects are planned to be treated in Part 1 of the study. Table 3-1 shows the probability to detect a significant effect under different true ORR i.e., Probability to have ORR ≥ 55% and the lower bound of the 95% CI > 35%. If the true ORR is 67% there is 91.7% probability that the single arm run-in part will be declared a success with 30 subjects.

Table 3-1 Design operating characteristics

True ORR	N	Minimum number of responses to declare success	ORR (95% CI)	Probability to reject H0
55%	30	17	56.7% (37.4 - 74.5)	50.2%
60%				71.5%
67%				91.7%

4 Change to protocol specified analyses

Not applicable.

5 Appendix

5.1 Imputation rules

5.1.1 Study drug

5.1.1.1 Data Imputation for the last administration

The following rule should be used for the imputation of date of last administration for a given study treatment component:

Scenario 1: If the date of last administration is completely missing and there is no EOT eCRF page, the subject is considered as on-going:

The subject should be considered as on treatment. In this case, the cut-off date should be used as the last dosing date for exposure calculations.

Scenario 2: If the date of last administration is completely or partially missing and the EOT eCRF page is available (prior to any death date or withdrawal of consent date, if available):

Case 1: The date of last administration is completely missing, and the EOT visit date is complete, then this latter date should be used.

Case 2: Only Year(yyyy) of the dose end date is available and yyyy < the year of EOT date:

Use Dec31yyyy

Case 3: Only Year(yyyy) of the dose end date is available and yyyy = the year of EOT date:

Use EOT date

Case 4: Both Year(yyyy) and Month (mm) are available for the date of last administration, and yyyy = the year of EOT date and mm < the month of EOT visit:

Use last day of the Month (mm).

After imputation, compare the imputed date with the start date of that specific record, if the imputed date is < start date of that record

Use the start date of that record.

Subjects with missing start dates are to be considered missing for all study treatment component related calculations described in Section 2.1.1.2 and no imputation will be made. If the date of first administration is missing, then the date of last administration should not be imputed.

5.1.1.2 Data Imputation of the first administration

Subjects with missing start dates are generally considered missing for all study treatment component related calculations described in Section 2.1.1.2 and no imputation will be made. If the date of first administration is missing, then the date of last administration should not be imputed.

5.1.2 AE date imputation

A missing AE start date will be imputed using the logic matrix described in Table 5-1

Table 5-1 Imputation rules for a partially missing AE start date

	AEM missing	AEM<TRTM	AEM=TRTM	AEM>TRTM
AEY missing	Not imputation	Not imputation	Not imputation	Not imputation
AEY<TRTY	(D)	(C)	(C)	(C)
AEY=TRTY	(B)	(C)	(B)	(A)
AEY>TRTY	(E)	(A)	(A)	(A)

AEM=Month AE started, AEY=Year AE started
TRTM=Month treatment started, TRTY=Year treatment started

Table 5-2 is the legend to the logic matrix shown in Table 5-1 and details the relationship of AE start date to study treatment start date.

Table 5-2 Imputation legend and AE/treatment start date relationship

AE start date relationship	Imputation
(A) After treatment start or uncertain	MAX(01MMMYYYY, TRTSDT+1)
(B) Uncertain	TRTSDT+1
(C) Before treatment start	15MMMYYYY
(D) Before treatment start	01JULYYYY
(E) After treatment start	01JANYYYY

Before treatment start: Partial date indicates AE start date is prior to treatment start date.
After treatment start: Partial date indicates AE start date is after treatment start date.
Uncertain: Partial date insufficient to determine relationship of AE start date to treatment start date.

No imputation will be performed for missing/incomplete AE end dates. AE with uncertain relationship will be considered as on-treatment AE.

5.1.3 Concomitant medication date imputation

The imputation of a concomitant medication start date will follow the same conventions as for an AE start date (see Section 5.1.2). No imputation will be performed for concomitant medication end dates.

5.1.3.1 Prior therapies date imputation

Start date

The same rule which is applied to the imputation of AE/concomitant medication start date will be used with the exception that scenario (B) will be replaced to be 'start date of study treatment - 1'. (see Section 5.1.2)

End date

Imputed date = min (start date of study treatment, last day of the month), if day is missing.

Imputed date = min (start date of study treatment, 31DEC), if month and day are missing.

If the end date is not missing and the imputed start date is after the end date, use the end date as the imputed start date.

If both the start date and the end date are imputed and if the imputed start date is after the imputed end date, use the imputed end date as the imputation for the start date.

5.1.3.2 Post therapies date imputation

Start date

Imputed date = max (End of Treatment date + 1, first day of the month), if day is missing.

Imputed date = max (End of Treatment date + 1, 01JAN), if day and month are missing.

Imputed date = End of treatment date +1, if the date is completely missing.

End date

No imputation

5.1.3.3 Other imputations

5.1.3.3.1 Diagnostic and extend of cancer

When a date is recorded as a partial date, the missing day is imputed to the 15th of the month (e.g., DEC2007 imputed to 15DEC2007), and if the day and month are both missing then to 1st of July of that year (e.g., 2007 imputed to 01JUL2007). Such imputed data will be flagged in the listings.

5.2 AEs coding/grading

Adverse events are coded using the Medical dictionary for regulatory activities (MedDRA) terminology. AEs will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

The CTCAE represents a comprehensive grading system for reporting the acute and late effects of cancer treatments. CTCAE grading is by definition a 5-point scale generally corresponding to mild, moderate, severe, life threatening, and death. This grading system inherently places a value on the importance of an event, although there is not necessarily proportionality among grades (a grade 2 is not necessarily twice as bad as a grade 1).

5.3 Laboratory parameters derivations

5.3.1 CTC grading for laboratory parameters

Grade categorization of lab values will be assigned programmatically as per NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. The calculation of laboratory CTC grades will be based on the observed laboratory values only, clinical assessments will not be taken into account. The criteria to assign CTC grades are given in Novartis internal criteria for CTC grading of laboratory parameters (see Table 5-3). The latest available version of the document based on the underlying CTCAE version 5.0 at the time of analysis will be used.

For laboratory tests where grades are not defined by CTCAE v5.0, results will be graded by the low/normal/high classifications based on laboratory normal ranges.

A severity grade of 0 will be assigned for all non-missing lab values not graded as 1 or higher. Grade 5 is not applicable. For laboratory tests that are graded for both low and high values, summaries will be done separately and labeled by direction, e.g., sodium will be summarized as hyponatremia and hypernatremia.

5.3.1.1 Imputation rules

CTC grading for blood differentials is based on absolute values. However, this data may not be reported as absolute counts but rather as percentage of WBC.

If laboratory values are provided as '<X' (i.e., below limit of detection) or '>X', prior to conversion of laboratory values to SI unit, these numeric values are set to X.

The following rules will be applied to derive the WBC differential counts when only percentages are available for a xxx differential

xxx count = (WBC count) * (xxx %value / 100)

Further derivation of laboratory parameters might be required for CTCAE grading. For instance, corrected calcium can be derived using the reported total calcium value and albumin at the same assessment using the following formula:

Corrected Calcium (mg/dL) = Calcium (mg/dL) – 0.8 [Albumin (g/dL)-4]

In order to apply the above formula, albumin values in g/L will be converted to g/dL by multiplying by 0.1), calcium values in mmol/L will be converted to mg/dL by dividing by 0.2495. For calculation of laboratory CTC grades 0 and 1, the normal range for derived corrected calcium is set to the same limits (in mg/dL) as for calcium.

Table 5-3 CTC grades v5.0 for laboratory values in Novartis Oncology

				CTC Grades[1]				
Lab test (toxicity)	**SI unit**	**Lab test (NCDS)**	**Normal ranges (Merck manual, July 2015) and *conversion factors***	**0**	**1**	**2**	**3**	**4**
Hematology								
WBC ↓ WBC (Leukocytosis)	10^9/L 10^9/L	WBC WBC	**3.9 – 10.7 x 10^9/L**	≥ LLN	< LLN - 3.0 x 10^9 /L -	< 3.0 – 2.0 x 10^9 /L -	< 2.0 – 1.0 x 10^9 /L > 100 x 10^9 /L	< 1.0 x 10^9 /L -
Hemoglobin (Anemia) Hemoglobin ↑	g/L g/L	HGB HGB	**120 - 160 g/L** or 7.4 - 9.9 mmol/L (F) **140 - 170 g/L** or 8.7 – 10.6 mmol/L (M) *(16.113 x mmol/L = g/L)*	≥ LLN	< LLN - 100 g/L < LLN - 6.2 mmol/L Increase >0-20 g/L above ULN	< 100 - 80 g/L < 6.2 - 4.9 mmol/L Increase >20-40 g/L above ULN	< 80 g/L < 4.9 mmol/L Increase >40 g/L above ULN	- -
Platelets ↓	10^9/L	PLAT	**150 - 350 x 10^9/L**	≥ LLN	< LLN - 75.0 x 10^9/L	< 75.0 - 50.0 x 10^9 L	< 50.0 - 25.0 x 10^9/L	< 25.0 x 10^9 /L
Neutrophils ↓	10^9/L	NEUT		≥2x10^9 /L	< 2.0 - 1.5 x 10^9 /L	< 1.5 - 1.0 x 10^9 /L	< 1.0 - 0.5 x 10^9 /L	< 0.5 x 10^9 /L
Lymphocytes ↓ Lymphocytes ↑	10^9/L 10^9/L	LYM LYM		≥1.5x10^9 /L	< 1.5 - 0.8 x 10^9 /L -	< 0.8 - 0.5 x 10^9 /L > 4 - 20 x 10^9 /L	< 0.5 - 0.2 x 10^9 /L > 20 x 10^9 /L	< 0.2 x 10^9 /L -
Biochemistry								
AST ↑	U/L	AST	**0 - 35 U/L** or 0 – 0.58 ukat/L *(60 x ukat/L = U/L)*	≤ ULN	> ULN – 3.0 x ULN	> 3.0 - 5.0 x ULN	> 5.0 - 20.0 x ULN	> 20.0 x ULN
ALT ↑	U/L	ALT	**0 - 35 U/L** or 0 – 0.58 ukat/L *(60 x ukat/L = U/L)*	≤ ULN	> ULN – 3.0 x ULN	> 3.0 - 5.0 x ULN	> 5.0 - 20.0 x ULN	> 20.0 x ULN
Total bilirubin ↑	umol/L	BILI	**5.1 – 20.5 umol/L** or 0.3 – 1.2 mg/dL *(17.1 x mg/dL = umol/L)*	≤ ULN	> ULN - 1.5 x ULN	> 1.5 - 3.0 x ULN	> 3.0 - 10.0 x ULN	> 10.0 x ULN
Alk. Phosphatase ↑	U/L	ALP	**36 - 92 U/L** or 0.5 - 1.5 ukat/L *(60 x ukat/L = U/L)*	≤ ULN	> ULN - 2.5 x ULN	> 2.5 - 5.0 x ULN	> 5.0 - 20.0 x ULN	> 20.0 x ULN
Creatinine ↑	umol/L	CREAT	**61.9 - 115 umol/L** or 0.7 – 1.3 mg/dL *(88.4 x mg/dL = umol/L)*	≤ ULN	> ULN - 1.5 x ULN	> 1.5 - 3.0 x ULN	> 3.0 - 6.0 x ULN	> 6.0 x ULN
Creatinine kinase ↑	U/L	CK	**30 – 170 U/L** or 0.5 – 2.83 ukat/L (60xukat/L=U/L)	≤ ULN	> ULN - 2.5 x ULN	> 2.5 - 5.0 x ULN	> 5.0 - 10.0 x ULN	> 10.0 x ULN
Albumin (Hypoalbuminemia)	g/L	ALB	**35 - 55 g/L** or 3.5 to 5.5 g/dL	≥ LLN	< LLN - 30 g/L	< 30 - 20 g/L	< 20 g/L	-

				CTC Grades[1]				
Lab test (toxicity)	**SI unit**	**Lab test (NCDS)**	**Normal ranges (Merck manual, July 2015) and *conversion factors***	**0**	**1**	**2**	**3**	**4**
Lipase ↑	U/L	LIPASE	**<95 U/L** or <1.58 ukat/L *(60 x ukat/L = U/L)*	≤ ULN	> ULN - 1.5 x ULN	> 1.5 - 2.0 x ULN	> 2.0 - 5.0 x ULN	> 5.0 x ULN
Amylase ↑	U/L	AMYLASE	**0 - 130 U/L** or 0 – 2.17 ukat/L *(60 x ukat/L = U/L)*	≤ ULN	> ULN - 1.5 x ULN	> 1.5 - 2.0 x ULN	> 2.0 - 5.0 x ULN	> 5.0 x ULN
Calcium (corrected) (Hypercalcemia)	mmol/L	CACALC	**2.2 - 2.6 mmol/L** or 9 - 10.5 mg/dL *(0.2495 x mg/dL = mmol/L)*	≤ ULN	> ULN - 11.5 mg/dL > ULN - 2.9 mmol/L	> 11.5 - 12.5 mg/dL > 2.9 - 3.1 mmol/L	> 12.5 - 13.5 mg/dL > 3.1 - 3.4 mmol/L	> 13.5 mg/dL > 3.4 mmol/L
Calcium (corrected) (Hypocalcemia)	mmol/L	CACALC		≥ LLN	< LLN - 8.0 mg/dL < LLN - 2.0 mmol/L	< 8.0 - 7.0 mg/dL < 2.0 - 1.75 mmol/L	< 7.0 - 6.0 mg/dL < 1.75 - 1.5 mmol/L	< 6.0 mg/dL < 1.5 mmol/L
Magnesium [2] (Hypermagnesemia)	mmol/L	MG	**0.62 – 0.99 mmol/L** or 1.5 – 2.4 mg/dL *(0.4114 x mg/dL = mmol/L)*	≤ ULN	> ULN - 3.0 mg/dL > ULN - 1.23 mmol/L	-	> 3.0 – 8.0 mg/dL > 1.23 – 3.3 mmol/L	> 8.0 mg/dL > 3.3 mmol/L
Magnesium [2] (Hypomagnesemia)	mmol/L	MG		≥ LLN	< LLN - 1.2 mg/dL < LLN - 0.5 mmol/L	< 1.2 - 0.9 mg/dL < 0.5 - 0.4 mmol/L	< 0.9 - 0.7 mg/dL < 0.4 - 0.3 mmol/L	< 0.7 mg/dL < 0.3 mmol/L
Glucose (Hypoglycemia)	mmol/L	GLUCSN/ GLUCSF		≥ LLN	< LLN - 55 mg/dL < LLN - 3.0 mmol/L	< 55 - 40 mg/dL < 3.0 - 2.2 mmol/L	< 40 - 30 mg/dL < 2.2 - 1.7 mmol/L	< 30 mg/dL < 1.7 mmol/L
Potassium (Hyperkalemia)	mmol/L	K	**3.5 - 5.0 mmol/L** *(0.2558 x mg/dL = mEq/L = mmol/L)*	≤ ULN	> ULN - 5.5 mmol/L	> 5.5 - 6.0 mmol/L	> 6.0 - 7.0 mmol/L	> 7.0 mmol/L
Potassium (Hypokalemia)	mmol/L	K		≥ LLN	< LLN - 3.0 mmol/L	-	< 3.0 - 2.5 mmol/L	< 2.5 mmol/L
Sodium (Hypernatremia)	mmol/L	SODIUM	**136 - 145 mmol/L** *(0.435 x mg/dL = mEq/L = mmol/L)*	≤ ULN	> ULN - 150 mmol/L	> 150 - 155 mmol/L	> 155 - 160 mmol/L	> 160 mmol/L
Sodium (Hyponatremia)	mmol/L	SODIUM		≥ LLN	< LLN - 130 mmol/L	-	< 130 - 120 mmol/L	< 120 mmol/L
Coagulation								
INR ↑	1	INR	**0.8 – 1.2**	≤ ULN	> ULN - 1.5 x ULN	> 1.5 - 2.5 x ULN	> 2.5 x ULN	-
Activated partial thromboplastin time ↑	sec	APTT	**25 - 35 sec**	≤ ULN	> ULN - 1.5 x ULN	> 1.5 - 2.5 x ULN	> 2.5 x ULN	-

ULN = Upper Limit of Normal range; LLN = Lower Limit of Normal range

LAB CTC grades 1, 2, 3, 4 overrule the study specific (central or local) normal range criteria, e.g., if ULN of Sodium is 151 mmol/L and the value is 151 mmol/L, CTC grade 2 is assigned although the value is ≤ ULN. **Life-threatening consequences and/or hospitalization are not considered** for determination of LAB CTC grades 3 and 4. Concomitant usage of anticoagulation therapy (for INR and Fibrinogen) is not considered either. Values and LNRs for blood differentials can be given as %, absolute values should then be calculated using WBC. Generally, ≥ **1.5 x 10^9 /L (lymphocytes) and ≥ 2 x 10^9 /L (neutrophils) are considered as LAB CTC grade 0.** For Creatinine and Fibrinogen, the **comparison with baseline is not considered** for derivation of LAB CTC grades.

6 Reference

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