NOVARTIS

Clinical Development

INC280/Capmatinib/Tabrecta®

CINC280A2204 / NCT04677595

A phase II, multicenter, two-cohort study of oral *MET* inhibitor capmatinib in Chinese adult patients with EGFR wild-type (wt), ALK rearrangement negative, *MET* exon 14 skipping mutations, advanced non-small cell lung cancer (NSCLC) who are treatment naive or failed one or two prior lines of systemic therapy

Statistical Analysis Plan (SAP) for Final Analysis

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List of abbreviations

AE	Adverse Event
AESI	Adverse Event of Special Interest
ALP	Alkaline Phosphatase
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/GPT
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
BID.	twice daily
BIRC	Blinded Independent Review Committee
BOIR	Best Overall Intracranial Response
BOR	Best Overall Response
CI	Confidence Interval
CNS	Central Nervous System
CR	Complete Response
CT	Computed Tomography
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating Tumor DNA
DAR	Drug administration record
DCR	Disease Control Rate
DNA	Deoxyribonucleic Acid
DOIR	Duration of Intracranial Response
DOR	Duration of Response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EGFR	Epidermal Growth Factor Receptor; also known as ErbB1
EORTC	European Organization for Research and Treatment of Cancer
EOT	End of Treatment
EQ-5D-5L	EuroQoL-5 Dimension-5 Level
FAS	Full Analysis Set
FDA	Food and Drug Administration
FPFV	First Participant First Visit
HR	Hazard Ratio
HRQoL	Health-Related Quality of Life
IDCR	Intracranial disease control rate
KM	Kaplan-Meier
LLOQ	Lower Limit of Quantification
LPLV	Last Participant Last Visit
MedDRA	Medical Dictionary for Drug Regulatory Affairs
METex14	MET exon 14 skipping
MRI	Magnetic Resonance Imaging
NSCLC	Non-Small Cell Lung Cancer
OIRR	Overall intracranial response rate
ORR	Overall Response Rate

OS	Overall Survival
PAS	Pharmacokinetic Analysis Set
PD	Progressive Disease
PFS	Progression-Free Survival
PK	Pharmacokinetics
PR	Partial Response
PT	Preferred Term
PRO	Patient-reported Outcomes
Q1	First Quartile (25th Percentile)
Q2	Second Quartile (50th Percentile, Median)
Q3	Third Quartile (75th Percentile)
QoL	Quality of Life
QTcF	Corrected QT interval using Fridericia correction
RANO-BM	Response Assessment in Neuro-Oncology Brain Metastases
RECIST	Response Evaluation Criteria in Solid Tumors

1 Introduction

This statistical analysis plan (SAP) describes the planned analyses for both Cohort 1 and Cohort 2 in the final clinical study report(s) (CSR) of study CINC280A2204, a phase II, multicenter, two-cohort study of oral MET inhibitor capmatinib in Chinese adult participants with EGFR wild-type (wt), ALK rearrangement negative, *MET* exon 14 skipping (METex14) mutations, advanced non-small cell lung cancer (NSCLC) who are treatment naive or failed one or two prior lines of systemic therapy.

The content of this SAP is based on protocol CINC280A2204 amended version 03 (dated 07-Jul-2022). All decisions regarding final analysis, as defined in the SAP document, have been made prior to database lock of the study data.

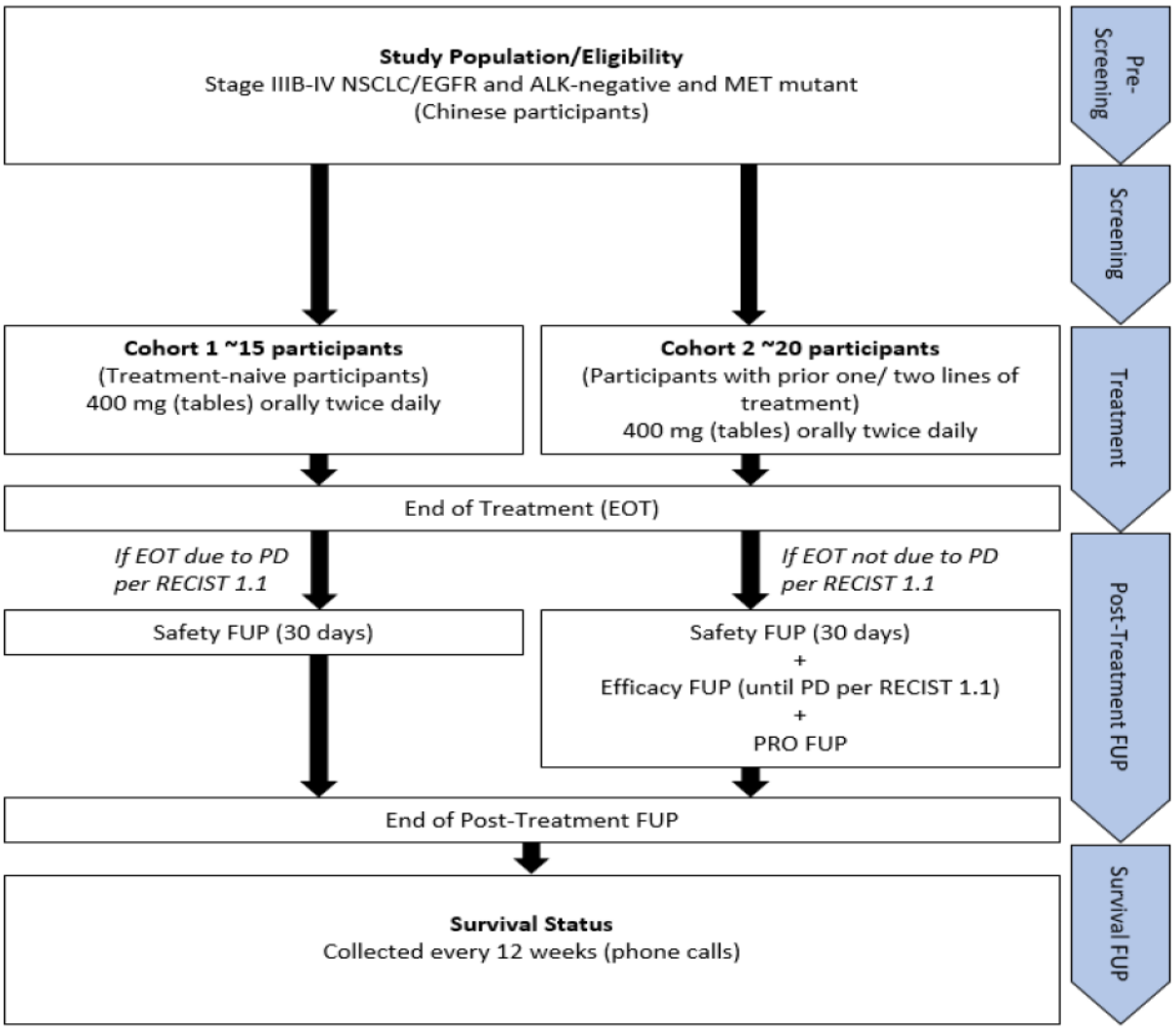
1.1 Study design

This is an open-label, multicenter two-cohort phase II study to evaluate the efficacy and safety of single-agent capmatinib in Chinese participants with EGFR wt (EGFR mutations that predict sensitivity to EGFR therapy, including, but not limited to exon 19 deletions and exon 21 L858R substitution mutations), ALK rearrangement negative, *MET* exon 14 skipping mutated advanced/metastatic NSCLC.

Approximately 35 participants aged 18 or over will be treated in this study in two separate cohorts. Cohort 1 will include approximately 15 treatment naive participants and Cohort 2 approximately 20 participants who failed one or two prior lines of therapy in the advanced stage. Each participant will receive 400 mg capmatinib tablet twice daily (BID).

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

Figure 1.1 Study Design



1.2 Study objectives and endpoints

The following study objectives and endpoints will be assessed in this study.

Table 1-1 Objectives and related endpoints

Objectives	Endpoints
Primary objective	**Endpoints for primary objective**
• To evaluate the antitumor activity of capmatinib, as measured by overall response rate (ORR) by blinded independent review committee (BIRC) assessment, by cohort	• ORR, proportion of participants with a best overall response (BOR) defined as complete response or partial response (CR+PR) by BIRC assessment per RECIST 1.1
Secondary objectives	**Endpoints of secondary objectives**

• To evaluate duration of response (DOR) as assessed by BIRC, by cohort	• DOR, calculated as the time from the date of the first documented CR or PR by BIRC per RECIST 1.1 to the first documented progression or death due to any cause for participants with PR or CR
• To evaluate ORR and DOR by investigator assessment, by cohort	• ORR (CR+PR) and DOR per RECIST 1.1 by investigator assessment
• To evaluate time to response (TTR), disease control rate (DCR) and progression-free survival (PFS) by investigator and by BIRC assessment, by cohort	• All calculated per RECIST 1.1, both by BIRC and investigator: – TTR, calculated as the time from first dose of capmatinib to first documented response (CR+PR) for participants with PR or CR – DCR, calculated as the proportion of participants with BOR of CR, PR, or SD – PFS, defined as time from first dose of capmatinib to progression or death due to any cause
• To evaluate overall survival (OS), by cohort	• OS, defined as time from first dose of capmatinib to death due to any cause
• To assess intracranial anti-tumor activity of capmatinib in participants with Central Nervous System (CNS) lesions at baseline by BIRC	• Overall intracranial response rate (OIRR), intracranial disease control rate (IDCR), time to intracranial response (TTIR), duration of intracranial response (DOIR) by BIRC as per RANO-BM criteria
• To evaluate the association between *METex14*mutation status as measured in ctDNA at baseline with capmatinib efficacy	• ORR, DOR and PFS per RECIST 1.1 for participants by *MET* mutation status assessed in ctDNA at baseline, both by BIRC and investigator
• To characterize the pharmacokinetics of capmatinib	• Steady state Ctrough and steady state 0.5-1.5 hour and 3-5 hours post-dose concentrations
• To evaluate capmatinib safety profile	• Incidence of adverse events (AEs) and serious adverse events (SAEs), change in vital signs, laboratory results (hematology, chemistry, and urinalysis) and ECG
• To assess the effect of capmatinib on patient-reported disease-related symptoms, functioning, and health-related quality of life (HRQoL)	• Change from baseline to each visit in European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 function, symptom, and impact domains/items; LC13 domain/items; and EuroQoL-5 Dimension-5 Level (EQ-5D-5L) health state utility values and VAS scores.

• To assess the effect of capmatinib on patient-reported symptoms of brain metastases	• Change from baseline to each visit in symptoms of brain metastases, with the NCCN FACT-Brain Symptom Index symptom module (FBrSI)

Analyses related to the secondary objectives listed below will not be repeated in the final analysis, as no data updated have occurred since the 12-month update analysis.

- To characterize the pharmacokinetics of capmatinib

2 Statistical methods

This section and its subsections will be used to draft CSR Section 9.7 on statistical analyses. The text will be changed to the past tense when imported into the CSR.

2.1 Data analysis general information

The final analysis will be performed by Novartis statistics and programming team. SAS version 9.4 or later will be used to perform all data analyses and to generate tables, figures and listings.

2.1.1 Data included in the analysis

All data with an assessment date or event start date (e.g. vital sign assessment date or start date of an adverse event) on or before the date of last patient last vist (LPLV) will be included in the analysis.

All events with start date before or on the date of LPLV and end date after the date of LPLV will be reported as 'ongoing'. The same rule will be applied to events starting before or on the cut-off date and not having documented end date. This approach applies, in particular, to adverse event and concomitant medication reports. For these events, the end date will not be imputed and therefore will not appear in the listings.

2.1.2 General analysis conventions

Pooling of centers: Unless specified otherwise, data from all study centers will be pooled for the analyses. Due to expected small number of subjects enrolled at centers, no center effect will be assessed. There is no stratification.

Qualitative data (e.g., gender, race) will be summarized by frequency counts and percentages. Percentages will be calculated using the number of participants in the relevant population or subgroup as the denominator.

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

2.1.3 General definitions

2.1.3.1 Study drug and study treatment

Study drug and study treatment both refer to INC280 (capmatinib) and will be used interchangeably.

2.1.3.2 Date of first administration of study drug

The date of first administration of study drug is defined as the first date when a non-zero dose of study drug was administered and recorded on the Dosage eCRF. For the sake of simplicity, the date of first administration of study drug will also be referred to as start date of study drug.

2.1.3.3 Date of last administration of study drug

The date of last administration of study drug is defined as the last date when a non-zero dose of study drug was administered and recorded on drug administration record (DAR) eCRF. This date will also be referred to as last date of study drug.

2.1.3.4 Study day

The study day for all assessments (e.g. tumor assessment, death, disease progression, tumor response, performance status, adverse event onset, laboratory abnormality occurrence, vital sign measurement, dose interruption) will be calculated using the start date of study drug as the origin. For assessments occurring after or on the start date of study drug, study day will be calculated as:

Study Day =Event date - start date of study drug + 1.

The first day of study drug is therefore study day 1.

For any assessment or events such as baseline disease characteristics or medical history (e.g., time since diagnosis of disease) occurring prior to the start of the study drug, study day will be negative and will be calculated as:

Study Day = Event date - start date of study drug.

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

2.1.3.5 Baseline

For efficacy evaluations, the last non-missing assessment, including unscheduled assessments on or before the date of first dose of study treatment is taken as “baseline” value or “baseline” assessment. In the context of baseline definition, the efficacy evaluations also include biomarkers, ECOG performance status and PROs.

For safety evaluations, the last available assessment on or before the date of start of study treatment is taken as “baseline” assessment.

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

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 values are from central and local laboratories, the value from central assessment should be considered as baseline. If multiple values are from the same local laboratory or collected, then the worst value should be considered as baseline.

2.1.3.6 Last contact date

The last contact date will be derived for participants not known to have died at the analysis cut-off using the last complete date among the following (Refer Table 2-1):

Table 2-1 Last contact date

Source data	Conditions
Last contact date/last date participant was known to be alive from Survival Follow-up page	Participant status is reported to be alive, lost to follow-up or unknown
Start/End dates from further antineoplastic therapy	Non-missing medication/procedure term.
Start/End* dates from drug administration record	Non-missing dose. Doses of 0 are allowed.
End of treatment date from end of treatment page	No condition.
Tumor assessment date	Evaluation is marked as 'done'.
Laboratory/PK collection dates	Sample collection marked as 'done'.
Vital signs 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 participant was seen or contacted on that date. 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 participants in the analysis of overall survival.

2.1.3.7 Time unit

For all derivations, a month will be calculated as (365.25 / 12) = 30.4375 days.

If duration is to be reported in years, duration in days will be divided by 365.25.

If duration is to be reported in months, duration in days will be divided by 30.4375.

If duration is to be reported in weeks, duration in days will be divided by 7.

2.1.3.8 On-treatment period/event and observation period

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

- **Pre-treatment period**: from the day of participant's informed consent to the day before first dose of study drug
- **On-treatment period:**
  - For discontinued participants, from day of first dose of study drug to 30 days after last dose of study drug
  - For ongoing participants, from day of first dose of study drug to the data cut-off date
- **Post-treatment period:** starting at day 31 after last dose of study drug

Safety summaries (tables, figures) and summaries of on-treatment death include only data from the on-treatment period with the exception of baseline data which will also be summarized

where appropriate (e.g. change from baseline summaries). In addition, a separate summary for death including on treatment and post treatment deaths will be provided. In particular, summary tables for adverse events (AEs) will summarize only on-treatment events, with a start date during the on-treatment period (***treatment-emergent*** AEs).

All data, regardless of observation period, will be listed and assessments collected in the post-treatment period will be flagged in all the listings.

2.2 Analysis sets

2.2.1 Full analysis set (FAS)

The full analysis set (FAS) comprises all participants to whom study treatment has been assigned and who received at least one dose of capmatinib. Unless otherwise specified, all efficacy analyses will be performed using FAS.

2.2.2 Full analysis set – brain metastases (FAS-BM)

The full analysis set - brain metastases (FAS-BM) comprises all participants in the FAS who have measurable and/or non-measurable brain metastases at baseline.

2.2.3 Per protocol set (PPS)

The PPS consists of a subset of participants in the FAS who have no major protocol deviations, who have an adequate tumor assessment at baseline and have a follow-up tumor assessment > 5 weeks after starting treatment (unless PD is observed before that time).

- The major protocol deviations that will lead to removal of participants from the PPS are listed below:
- Participant does not have Stage IIIB, IIIC or IV NSCLC (any histology) at the time of study entry
- Participant does not have a histologically or cytologically confirmed diagnosis of NSCLC
- Participant with EGFR+, ALK+ or other known druggable molecular alterations (such as ROS1 translocation or BRAF mutation, etc.) which might be a candidate for alternative targeted therapies as applicable per local regulations and treatment guidelines
- Participant without METexon14 skipping mutation for eligibility as determined by central assessment at a Novartis designated laboratory prior to first dose
- Participant has not received one or two prior lines of systemic therapy for advanced/metastatic disease (only for cohort 2)
- Participant has received prior systemic therapy for advanced/metastatic disease (only for cohort1)
- Participant has no measurable lesion from RECIST 1.1 evaluation at baseline or has no baseline evaluation by Investigator
- Participant has received crizotinib, or any other MET or HGF inhibitor before entering screening

- ECOG performance status > 1 at study entry

2.2.4 Safety set

The Safety Set includes all participants who received at least one dose of capmatinib. Unless otherwise specified, all safety data will be analyzed by Safety Set.

2.2.5 Subgroup of interest

Due to small sample size in each cohort, no formal subgroup analyses are planned. If any subgroup analyses will be needed for further exploration, subgroup analyses will be performed separately and separate analysis plan will be developed.

2.3 Participants disposition, demographics and other baseline characteristics

2.3.1 Participants disposition

The FAS will be used for the subject disposition summary tables by cohort. The FAS will be used for the listings by cohort.

The following will be tabulated:

- Number (%) of participants who are still on-treatment (based on "Treatment disposition")
- Number (%) of participants who discontinued treatment (based on "Treatment disposition" and "Participant status")
- Number (%) of participants who entered post-treatment efficacy follow-up (based on "Post-treatment follow-up disposition" and "Treatment disposition")
- Number (%) of participants who entered survival follow-up (based on completion of 'Subject Status' and "Post-treatment follow-up disposition")
- Number (%) of participants who discontinued from study (based on completion of 'Study Phase Disposition' page with date of discontinuation and discontinuation reasons entered under 'Subject Status' and 'Will subject continue into the next phase of the trial' is 'No' for participants who discontinued from the post-treatment efficacy follow-up)
- Primary reasons for discontinuation from the post-treatment efficacy follow-up (based on discontinuation reasons entered under 'Subject Status' in the 'Study Phase Disposition' page).

2.3.2 Basic demographic and background data

All demographic and baseline disease characteristics data will be summarized and listed by cohort. Categorical data (e.g. gender, ECOG performance status) will be summarized by frequency count and percentages. Continuous data (e.g. age, weight, height, BMI) will be summarized by descriptive statistics using FAS.

2.3.3 Diagnosis and extent of cancer

Summary statistics will be tabulated for diagnosis and extent of cancer by cohort using FAS. This analysis will include the followings: primary site of cancer, stage at initial diagnosis, stage

at time of study entry, time (in months) since most recent relapse/progression, histological grade, predominant histology/cytology, types of lesions (target and non-target lesions) at baseline, number of target lesions at baseline, and disease burden at baseline for target lesion (based on the data collected on the RECIST eCRF page) and other relevant information if collected.

2.3.4 Medical history

Medical history and ongoing conditions, including cancer-related conditions and symptoms will be summarized and listed by cohort using FAS. Separate summaries will be presented for ongoing and historical medical conditions. The summaries will be presented by primary system organ class (SOC) and preferred term (PT). Medical history and current medical conditions are coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The MedDRA version used for reporting will be specified in the CSR and as a footnote in the applicable tables/listings.

2.3.5 Screen failures

Screen failures are participants who have been enrolled and have failed to meet inclusion or exclusion criteria. These participants are not treated with study drug. Frequency counts and percentages will be tabulated for all enrolled participants by cohort as follows:

- Number (%) of participants who completed screening phase (based on the presence of study phase completion date and the 'Next phase entered' is 'Treatment' in the 'Screening Phase Disposition' page);
- Number (%) of participants who discontinued during screening phase (based on the presence of date of discontinuation and discontinuation / "subject status" reason entered and 'Will the participant continue into the next phase of the trial' is 'No' in the 'Screening Phase Disposition' page);
- Reasons for screening phase discontinuation (based on reasons recorded in Screening Phase Disposition' page).

All screen failure participants with reasons for screen failure will be listed by cohort.

2.4 Protocol deviations

The number (%) of subjects in the FAS with any protocol deviation will be tabulated by deviation category (as specified in the edit-check specification) overall and by cohort for the FAS. All protocol deviations will be listed.

The outbreak of the Covid-19 pandemic may neccesiate some changes to the study conduct such that the protocol could not be followed strictly. To understand the effect of the pandemic on the execution and outcome of the study, deviations will be identified and recorded as protocol deviations.

In addition to the pre-defined standard PD terms, Novartis has defined 6 new protocol deviations and the corresponding relationship (health status related vs. site lockdown, participant concern, etc.) to the COVID-19 pandemic in line with "FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency" (March

2020) and "Guidance on the management of clinical trials during the COVID-19 (coronavirus) pandemic" (April 2020) from EMA as listed below.

- Missing visits
- Changes in procedures and assessments
- Planned visits not done at sites
- Changes in drug supply method
- Treatment not given
- Participant's discontinuation due to COVID-19 situation

The COVID-19 related protocol deviations will be summarized separately by cohort if applicable.

2.5 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

2.5.1 Study treatment / compliance

Study drug and study treatment

Study drug and study treatment both refer to INC280 and will be used interchangeably.

Dose exposure and intensity

Definitions of duration of exposure, cumulative dose, average daily dose, dose intensity (DI), relative dose intensity (RDI), as well as intermediate calculations, include:

- Duration of exposure (days): last date of study drug − first date of study drug + 1 (periods of interruption are not excluded)
- Cumulative dose (mg): total dose of study drug taken by a participant in the study
- Number of dosing days (days): duration of exposure − number of zero dose days
- Average daily dose (mg/day): cumulative dose (mg)/number of dosing days (days)
- DI (mg/day): cumulative dose (mg)/duration of exposure (days)
- PDI (mg/day) planned cumulative dose (mg)
- RDI (%): 100 × [DI (mg/day)/PDI (planned dose (800 mg/day)]

Note: Because the planned INC280 dose is 800 mg/day, or the planned dose intensity (PDI) is 800 mg/day, RDI (%) can be calculated by 100*DI/PDI and simplified as shown above.

Duration of study exposure to study drug, cumulative dose, average daily dose, DI and RDI will be summarized by cohort. In addition, the duration of exposure to study drug will be categorized into time intervals and frequency counts and percentages of participants with exposure in each time interval will be presented.

2.5.2 Dose interruptions or permanent discontinuations

Frequency counts and percentages of participants who have dose changes, reductions or interruptions, and the corresponding reasons, will be summarized by cohort.

An analysis of time to first interruption (in weeks) will be presented based on simple descriptive statistics (not using time-to event methods).

Time to first interruption is the time from date of first administration of study drug to the first date when a zero dose of study drug is recorded on the DAR eCRF, expressed in weeks.

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 and mentioned in multiple entries on consecutive days, then it will be counted as one interruption.

Listings of all doses of the study drug along with dose change and dose interruption reasons will be produced by cohort.

Section 5.2 provides further details on the definition of dose changes and interruptions.

2.5.3 Prior, concomitant and post therapies

2.5.3.1 Prior anti-cancer therapy

The number and percentage of participants who received any prior anti-neoplastic medications, prior anti-neoplastic radiotherapy or prior anti-neoplastic surgery will be summarized by cohort.

Prior anti-neoplastic medications will be summarized by chemotherapy (medication) setting, other therapy (medication) setting, number of prior regimens of anticancer medications and prior anticancer medications. Prior antineoplastic medications will also be summarized by ATC class, and preferred term. The medication therapy type of any combination therapy will be classified based on the following order: immunotherapy, chemotherapy, biologic therapy (other than immunotherapy), targeted therapy. For example, a combination therapy of chemotherapy and immunotherapy will be classified as 'immunotherapy'.

Prior anti-neoplastic medications for therapeutic setting (any line, 1st line, 2nd line) will be summarized by line: single agent chemotherapy, Platinum based chemotherapy, immunotherapy, chemotherapy in combination with immunotherapy.

For radiotherapy, time since last radiotherapy, locations and setting of last therapy will be summarized.

For prior surgery, time since last surgery, procedure and residual disease of last therapy will be summarized.

All the above analyses will be performed separately by cohort.

Prior anti-neoplastic therapy will be listed by cohort in three separate listings:

1. Medications
2. Radiotherapy
3. Surgery

2.5.3.2 Concomitant therapy

Concomitant therapies are defined as any medications (excluding study drug, prior antineoplastic treatments and blood transfusions), surgeries, palliative radiotherapies or

procedures (including physical therapy) administered in the study and are recorded in the Prior and Concomitant Medications and the Surgical and Medical Procedures eCRF, respectively.

Concomitant medications will be coded using the WHO Drug Reference Listing (WHO DRL) dictionary that employs the WHO Anatomical Therapeutic Chemical (WHO ATC) classification system. Surgeries or procedures will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology. All summaries will be tabulated using frequency counts and percentages.

Concomitant therapies will be summarized by ATC class, preferred term and cohort. Surgical and medical procedures will be coded using MedDRA and summarized by SOC and preferred term. These summaries will include: 1) medications starting on or after the start of study drug but starting no later than 30 days after last dose of study drug and 2) medications starting prior to the start of study drug but continuing after the start of study drug.

All concomitant therapies will be listed by cohort. Any concomitant therapies starting and ending prior to the start of study drug or starting more than 30 days after the last date of study drug will be flagged in the listings.

2.5.3.3 Antineoplastic therapy after discontinuation of study drug

The FAS will be used for all listings and summaries of antineoplastic therapies initiated after discontinuation of study drug. All summaries will be tabulated using frequency counts and percentages by cohort.

Antineoplastic medications initiated after discontinuation of study drug will be summarized and listed by Anatomical Therapeutic Chemical (ATC) class, preferred term and cohort.

Antineoplastic radiotherapy since discontinuation of study treatment will be summarized and listed by setting and cohort.

Antineoplastic surgery since discontinuation of study treatment will be summarized and listed by SOC and preferred term and cohort.

2.6 Analysis of the primary objective

2.6.1 Primary endpoint

The primary objective is to demonstrate the antitumor activity of INC280, as measured by overall response rate (ORR) to INC280 by Blinded Independent Review Committee (BIRC) assessment, by cohort.

2.6.2 Primary estimand

The primary scientific question of interest is: What is the effect of capmatinib in inducing radiological response by blinded independent review committee (BIRC) as per response evaluation criteria in solid tumors (RECIST) 1.1 in Chinese participants who are either treatment naive or failed one or two prior lines of systemic therapy with METΔex14 mutation, regardless of study treatment discontinuation and prior to start of new anti-neoplastic therapy by cohort?

The primary estimand will be described by the following five attributes:

1. The **population** is the adult Chinese paticipants with EGFR wild-type(wt), ALK rearrangement negative, MET exon 14 skipping mutations advanced non-small cell lung cancer (NSCLC) who are either treatment naive or failed one or two prior lines of systemic therapy
2. The treatment attribute is the oral dose of Capmatinib 400 mg administered i.e. total dose of 800 mg daily
3. The variable is the best overall response (BOR) by cohort defined as the best response recorded from the date of treatment start until disease progression/recurrence (taking as reference for PD, the smallest measurement recorded since the treatment started) based on BIRC per RECIST 1.1. prior to start of any neoantiplastic therapy
4. The **intercurrent events** of interest are
    a. The treatment discontinuation for any reason: tumor assessment data collected irrespectively of treatment discontinuation will be included to derive BOR (treatment strategy)
    b. Start of neoantiplastic therapy: any tumor response after the antineoplastic therapy will be considered as non-responser (composite strategy)
    c. Any public health emergency as declared by local or regional authories i.e. pandemic, epidemic or natural disaster: assessment collected irrespectively of those events will be included to derive BOR (treatment policy strategy)
5. The summary measure is the overall best overall response rate (ORR) and its exact 95% confidence interval (CI) (Clopper and Pearson 1934) will be provided by cohort.

2.6.2.1 Statistical hypothesis, model, and method of analysis

The analysis of primary endpoint will be performed on the FAS. The primary efficacy endpoint ORR will be estimated and the exact 95% confidence interval (CI) (Clopper and Pearson 1934) will be provided by cohort.

The study is based on estimation of the endpoint and therefore **no statistical hypothesis** test will be performed.

2.6.2.2 Handling of intercurrent events of primary estimand

Tumor assessment data collected irrespective of treatment discontinuation until the start of new anti-cancer therapy will be included to derive BOR.

If any new anti-cancer therapy is taken, any subsequent assessments would be excluded from the BOR determination. In case of any missed visit due to health emergencies as declared by local authorities (pandemic, epidemic or natural disaster) will be included for the BOR calculation.

2.6.2.3 Handling of missing values/censoring/discontinuations

Confirmed PR or CR reported prior to any additional anticancer therapy will be considered as responses in the calculation of the ORR irrespective of the number of missed assessments before response.

Participants with a BOR of ‘Unknown’ per RECIST 1.1 will be considered as non-responders when estimating ORR.

Participants with no BIRC data will be considered as non-responders when estimating ORR.

Participants who have disease progression and continue to receive study drug after progression will qualify for PD at the time of progression and will be counted as PD in the derivation of ORR and any other efficacy endpoints.

2.6.3 Supportive analyses

ORR by BIRC will be summarized by PPS to support the primary analysis.

2.7 Analysis of secondary objective(s)

2.7.1 Efficacy secondary endpoints

2.7.1.1 Duration of response (DOR)

DOR only applies to participants whose BOR is complete response (CR) or partial response (PR) according to RECIST 1.1 based on tumor response data. The start date is the date of first documented response of CR or PR (i.e. the start date of response, not the date when response was confirmed), and the end date is defined as the date of the first documented progression or death due to any cause. DOR will be assessed as per BIRC review and by investigator assessment for both FAS and PPS.

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

Table 2-2 Outcome and event dates for DOR and PFS analyses

	Situation	Date	Outcome
A	No baseline assessment	Date of first dose of study drug [a]	Censored
B	Progression at or before next scheduled Assessment	Date of progression	Progressed
C1	Progression or death after exactly one missing assessment	Date of progression (or death)	Progressed
C2	Progression or death after two or more missing assessments	Date of last adequate assessment	Censored
D	No progression	Date of last adequate assessment	Censored
E	Treatment discontinuation due to 'Disease progression' without documented progression, i.e. clinical progression based on investigator claim	N/A	Information ignored. Outcome derived based on radiology data only.
F	New anticancer therapy given	Ignore the new anticancer therapy and follow situations above	As per above situations
G	Deaths due to reason other than deterioration of 'Study indication'	Date of death	Progressed

[a] The rare exception to this is if the participant dies no later than the time of the second scheduled assessment as defined in the protocol in which case this is a PFS event at the date of death

The date of last adequate tumor assessment is the date of the last tumore assessment with overall lesion response of CR, PR, SD, or non-CR/non-PD before an event or a censoring reason occurred. In this case, the last tomor evaluation date at that assessment will be used. Participants without a post-baseline tumor assessment will be censored at the time of the first treatment.

DOR will be described in tabular and graphical format using Kaplan-Meier methods by cohort. In the Kaplan-Meier plot the number of participants at risk at certain time points will be shown on the plot. The estimated median (in months) along with 95% CIs, as well as 25th and 75th percentiles will be reported (Brookmeyer and Crowley 1982). In addition, Kaplan-Meier estimated probabilities with corresponding 95% CIs at several time points (including at least 3, 6, 12, and 18 months) will be summarized. These analyses will be performed separately based on BIRC assessment and based on investigator assessment.

2.7.1.2 ORR by investigator assessment

The evaluation of ORR will be also conducted based on investigator assessment. ORR will be estimated and the exact binomial 95% CI will be provided by cohort. The same process described in section 2.6.1 will be followed to evaluate ORR.

2.7.1.3 Time to response (TTR)

TTR is defined as the time from the date of start of study drug to the first documented response of either complete response (CR) or partial response (PR), which must be subsequently confirmed (although date of initial response is used, not date of confirmation). TTR will be evaluated as per BIRC and also by investigator review and according to RECIST 1.1.

Participants without a confirmed CR or PR will be censored at the study-maximum follow-up time (i.e. first participant first visit (FPFV) to last participant last visit (LPLV)) for participants with a PFS event (i.e. disease progression or death due to any cause), or at the date of the last adequate tumor assessment for participants without a PFS event.

TTR will be summarized in 6-weeks intervals using descriptive statistics by cohort. The distribution of time to response will be estimated using the Kaplan-Meier method and the median time to response will be presented along with 95% confidence interval only if a sufficient number of responses is observed. Failure curves (ascending Kaplan-Meier curves) will be constructed. These analyses will be performed separately based on BIRC assessment and based on investigator assessment.

2.7.1.4 Disease control rate (DCR)

DCR is defined as the proportion of participants with best overall response of CR, PR, or SD per RECIST 1.1. DCR will be estimated and the binomial exact 95% CI will be provided by cohort. These analyses will be performed separately based on BIRC assessment and based on investigator assessment.

2.7.1.5 Progression-free survival (PFS)

PFS is defined as the time from the start date of study drug to the date of the first radiologically documented PD or death due to any cause.

If a participant has not progressed or is not known to have died at the date of analysis cut-off, PFS will be censored at the date of the last adequate tumor evaluation before the cut-off date. PFS events documented after the initiation of neoantineoplastic therapy will be considered provided tumor assessments continue after initiation of the new cancer therapy. Clinical deterioration will not be considered as a qualifying event for progression. Refer to Table 2-2 for censoring and event date options and outcomes for PFS.

PFS will be described in tabular and graphical format using Kaplan-Meier methods as described for DOR by cohort, including estimated median (in months) with 95% CI, 25th and 75th percentiles and Kaplan-Meier estimated probabilities with corresponding 95% CIs at several time points. Censoring reasons will also be summarized by cohort.

These analyses will be performed separately based on BIRC assessment and based on investigator assessment.

2.7.1.6 Overall survival (OS)

OS is defined as the time from the start date of study drug to the date of death due to any cause. If the participant is alive at the date of the analysis cut-off or lost to follow-up, then OS will be censored at the last contact date prior to data cutoff date (see Section 2.1.3.6) for further details on derivation of last contact date).

OS will be described in tabular and graphical format using Kaplan-Meier methods as described for DOR by cohort, including estimated median (in months) with 95% CI, 25th and 75th percentiles and Kaplan-Meier estimated probabilities with corresponding 95% CIs at several time points. Censoring reasons will also be summarized by cohort.

2.7.1.7 Overall intracranial response rate (OIRR)

OIRR is calculated based on response assessments in the brain for participants having measurable and/or non-measurable brain metastases at baseline. OIRR is the proportion of participants with a confirmed best overall intracranial response (BOIR) of CR or PR from the start of treatment until disease progression /recurrence (taking as reference for PD the smallest measurements recorded since the treatment started) per RANO-BM criteria as assessed by BIRC review (See Reference)

The BOIR for each participant is determined from the sequence of overall (lesion) responses according to the following rules:

- CR = at least two determinations of CR at least 4 weeks apart before progression where confirmation required or one determination of CR prior to progression where confirmation not required
- PR = at least two determinations of PR or better at least 4 weeks apart before progression (and not qualifying for a CR) where confirmation required or one determination of PR prior to progression where confirmation not required
- SD = at least one SD assessment (or better) > 6 weeks after start of treatment (and not qualifying for CR or PR).
- PD = progression ≤ 12 weeks after start of treatment (and not qualifying for CR, PR or SD).

- Not evaluable (NE) = all other cases (i.e. not qualifying for confirmed CR or PR and without SD after more than 6 weeks or early progression within the first 12 weeks)

While evaluating for the OIRR, the followings will be considered:

- any assessments taken more than 30 days after the last dose of study treatment will not be included in the best overall intracranial response derivation.
- any alternative cancer therapy taken while on study any subsequent assessments would ordinarily be excluded from the best overall intracranial response determination.

OIRR calculated based on the data from the FAS-BM and the corresponding 95% CI based on the exact binomial distribution (Clopper and Pearson 1934) will be presented by cohort.

In case of very limited participants will be experiencing brain metastasis, only listing by cohort will be provided.

2.7.1.8 Intracranial disease control rate (IDCR)

IDCR is calculated based on response assessments in the brain for participants having measurable and/or non-measurable brain metastases at baseline. IDCR is the proportion of participants with a confirmed BOIR of CR or PR or SD (or non-CR/non-PD) per RANO-BM criteria as assessed by BIRC review.

IDCR calculated based on the data from the FAS-BM and the corresponding 95% CI based on the exact binomial distribution (Clopper and Pearson 1934) will be presented by cohort.

In case of very limited participants will be experiencing brain metastasis, only listing by cohort will be provided.

2.7.1.9 Time to intracranial response (TTIR)

TTIR is defined as the time from the date of the start of study treatment to the date of the first documented intracranial response of either CR or PR per RANO-BM criteria as assessed by the BIRC review, which must be subsequently confirmed (date of initial response is used, not date of confirmation).

All participants in the FAS-BM will be included in TTIR calculations. Participants without a confirmed intracranial CR or PR will be censored at the study-maximum follow-up time (i.e. LPLV−FPFV), for participants with an intracranial PFS event (intracranial progression or death due to any cause), or at the date of the last adequate tumor assessment in brain for participants without an intracranial PFS event.

Median TTIR with corresponding 95% CI, and 25th and 75th percentiles (Brookmeyer and Crowley 1982) will be presented. TTIR will be summarized using the KM method, based on data from the FAS-BM. KM estimates for TTIR proportions at specific time points, along with 95% CI will also be provided by cohort.

In case of very limited participants will be experiencing brain metastasis, only listing by cohort will be provided.

2.7.1.10 Duration of intracranial response (DOIR)

DOIR only applies to participants whose confirmed BOIR is CR or PR per RANO-BM criteria as assessed by the BIRC review. DOIR is defined as the time from the date of first documented intracranial response of either CR or PR to the date of the first documented intracranial progression per RANO-BM criteria as assessed by BIRC review or date of death due to any cause.

Participants with a confirmed intracranial CR or PR will be censored if they have disease progression in organs other than brain and have no scans in brain after that. Participants will also be censored for death due to other causes. The censoring date will be the date of the last adequate tumor assessment in brain.

Table 2-3 Outcome and event dates for DOIR

	Situation	Date	Outcome
A	No baseline assessment in the brain	Date of first dose of study drug [a]	Censored
B	Intracranial progression at or before next scheduled assessment	Date of intracranial progression	Progressed
C1	Intracranial progression or death after exactly one missing assessment	Date of intracranial progression (or death)	Progressed
C2	Intracranial progression or death after two or more missing assessments	Date of last adequate tumor assessment in the brain	Censored
D	No intracranial progression including disease progression (RECIST) in organs other than brain and have no scans in brain after that	Date of last adequate assessment in the brain	Censored
E	Treatment discontinuation due to 'Disease progression' without documented progression, i.e. clinical progression based on investigator claim but no intracranial progression and no brain scan after that	Date of last adequate tumor assessment in the brain	Censored
F	New anticancer therapy given	Ignore the new anticancer therapy and follow situations above	As per above situations
G	Deaths due to reason any cause	Date of death	Progressed

The rare exception to this is if the participant dies no later than the time of the second scheduled assessment as defined in the protocol in which case this is a PFS event at the date of death

DOIR will be summarized using the KM method. Median DOIR, with corresponding 95% CI, and 25th and 75th percentiles (Brookmeyer and Crowley 1982) will be presented. KM estimates for DOIR proportions at specific time points, along with 95% CI will also be provided by cohort.

In case of very limited participants will be experiencing brain metastasis, only listing by cohort will be provided.

2.7.2 Sensitivity analysis

Sensitivity analysis will be performed for DOR and PFS. In the sensitivity analysis of DOR and PFS, for subjects who receive antineoplastic therapy, the event will be censored at the last tumor assessment prior to the antineoplastic therapy. Every other event/censoring criteria on Table 2.2 will remain the same.

2.8 Safety analyses

For all safety analyses, the safety set will be used. All listings and tables will be presented by cohort.

2.8.1 Adverse events (AEs)

AEs will be coded using MedDRA using the latest version available prior to clinical database lock and will be graded using Common Terminology Criteria for Adverse Events (CTCAE) version 5 or higher. If CTCAE grading does not exist for an AE, grades 1, 2, 3, 4, and 5 corresponding to the severity of mild, moderate, severe, life-threatening, and death, respectively, will be used.

All AE summaries will be summarized (frequency counts and percentages) by system organ class and/or preferred term, and maximum severity grades, except where otherwise noted. A participant with multiple CTC grades for an AE will be summarized under the maximum CTC grade recorded for the event.

The following AE summaries will be produced:

- AEs regardless of study drug relationship
- AEs suspected to be study drug related
- SAEs regardless of study drug relationship
- SAEs suspected to be study drug related
- AEs leading to permanent study drug discontinuation of study drug regardless of study drug relationship
- AEs leading to permanent study drug discontinuation of study drug suspected to be study drug related
- AEs requiring dose adjustment and/or study drug interruption regardless of study drug relationship
- AEs requiring dose adjustment and/or study drug interruption suspected to be study drug related
- AEs requiring significant additional therapy regardless of study drug relationship
- AEs requiring significant additional therapy suspected to be study drug related
- AEs excluding SAEs

In addition, a summary of serious adverse events with number of occurrences will be produced (an occurrence is defined as >1 day between start and prior end date of record of same preferred term).

2.8.1.1 Adverse events of special interest / grouping of AEs

An adverse event of special interest is a grouping of adverse events that are of scientific and medical concern specific to compound INC280. These groupings are defined using MedDRA terms, SMQs (standardized MedDRA queries), HLGTs (high level group terms), HLT (high level terms) and PTs (preferred terms). Customized SMQs (Novartis MedDRA queries, NMQ) may also be used. An 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.

All AESI definitions or AE grouping are specified in the electronic Case Retrieval Strategy (eCRS), in which they are identified by the flag "SP". Additional AESI may be reported if there are any updates to the eCRS at the time of the analyses.

Adverse events of special interest (AESIs) INC280 are:

- Hepatotoxicity
- Renal dysfunction
- ILD/Pneumonitis
- Central nervous system toxicity
- Pancreatitis
- Phototoxicity
- Teratogenicity
- Drug-drug interactions with strong CYP3A4 inducers
- QTc interval prolongation

For each specified AESI, number and percentage of participants with at least one event of the AESI occurring during on treatment period will be summarized.

Summaries of these AESIs will be provided by cohort, (specifying grade, SAE, relationship, leading to permanent treatment discontinuation, leading to dose adjustment/interruption, death, etc.).

2.8.2 Deaths

Separate summaries for on-treatment and all deaths will be produced by cohort, system organ class and preferred term.

All deaths will be listed, post treatment deaths will be flagged. A separate listing of deaths prior to starting treatment will be provided for all screened participants.

2.8.3 Laboratory data

Laboratory data assessments will be performed locally. The summaries will include all laboratory assessments collected no later than 30 days after study drug discontinuation. All laboratory assessments will be listed and those collected later than 30 days after study drug discontinuation will be flagged in the listings.

Laboratory data will be classified (by Novartis Oncology Statistical Programming) into CTC grades according to the NCI CTCAE v5.0. For all reports, CTC grade is always obtained on the converted measurement in SI unit. The CTC grade 0 will be assigned as below in different scenarios:

- For lab parameters defined by criteria based on normal range only, a severity grade of 0 will be assigned when the value is within normal limits.
- For lab parameters whose grade is defined by criteria based on normal range and absolute values (e.g. platelet count decrease). A severity grade of 0 will be assigned when the value is within normal limits.
- For lab parameters whose grade is defined by criteria based on normal range and the change from baseline value, with no other associated clinical criteria such as concomitant medication (e.g. creatinine increased) the following will be applied. For the baseline grading and for the grading of post-baseline lab values with missing baseline grading, the grade will be derived using the criteria based only on the normal range as per NCI CTCAE version v5.0. A severity grade of 0 will be assigned when the post-baseline value is $\leq$ ULN (for hyper) or $\geq$ LLN (for hypo).

Parameters for which a grading does not exist will be classified into low/normal/high group by means of laboratory normal ranges.

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

- Shift tables using CTC grades to compare baseline to the worst post-baseline value for laboratory parameters with CTC grades
- Shift tables using low, normal, high (as well as low and high combined) classifications to compare baseline to the worst post-baseline value for laboratory parameters where CTC grades are not defined.
- New or worsened abnormalities for laboratory parameters based on CTC grade
- Trends of renal function parameters (creatinine, urea) over time (baseline and selected on-treatment time-points) will be displayed via boxplots based on time windows and corresponding tables displaying the statistics used for the box plots by the selected time points.

The following lab parameters will be summarized by cohort:

- Hematology: absolute lymphocytes, absolute neutrophils, hemoglobin (anemia), WBC, platelet counts, absolute basophils, absolute eosinophils, absolute monocytes, hematocrit
- Biochemistry: alkaline phosphatase (ALP), SGPT (ALT), SGOT (AST), total bilirubin, amylase, potassium, sodium, creatinine, glucose (hypo only), phosphate, albumin, calcium, magnesium, creatinine, direct bilirubin, blood urea nitrogen (BUN) or urea, GGT, lipase.
- For bi-directional parameters, both hyper and hypo summaries will be presented.

The following laboratory parameters will be presented in listings and will not be summarized:

- Urinalysis: macroscopic panel (dipstick) (bilirubin, blood, glucose, WBC, pH, protein, specific gravity), Urinalysis Microscopic panel (RBC, WBC, casts).
- Coagulation: INR, pro-thrombin time (PT) or Quick Test

The following listings will be produced for the laboratory data for all laboratory parameters where CTC grades are defined:

- Listing of participants with laboratory abnormalities of CTC grade 3,4, or 5
- Listing of all laboratory data with values flagged to show the corresponding CTC grades and the classifications relative to the laboratory reference ranges.

Liver function parameters

Liver function parameters of interest are total bilirubin (BILI), ALT, AST and alkaline phosphatase (ALP). The number and percentage of participants with worst post-baseline values as per Novartis Liver Toxicity guideline will be summarized by cohort. Because the study protocol inclusion criteria allowed participants to be enrolled with elevated baseline ALT or AST values, these are distinguished in the assessment.

The following summaries will be produced:

- Peak post-baseline values
  - ALT >3×ULN
  - ALT >5×ULN
  - ALT >10×ULN
  - ALT >20×ULN
  - AST >3×ULN
  - AST >5×ULN
  - AST >10×ULN
  - AST >20×ULN
  - ALT or AST >3×ULN
  - ALT or AST >5×ULN
  - ALT or AST >8×ULN
  - ALT or AST >10×ULN
  - ALT or AST >20×ULN
  - BILI >2×ULN
  - BILI >3×ULN
- Combined elevations post-baseline
  - AST and ALT ≤ ULN at baseline
    - (ALT or AST >3×ULN) and BILI >2×ULN
    - (ALT or AST >3×ULN) and BILI >2×ULN and ALP ≥ 2×ULN
    - (ALT or AST >3× ULN) and BILI >2× ULN and ALP <2×ULN
  - ALT or AST >ULN at baseline
    - (Elevated ALT or AST) and BILI >2×BL and BILI >2×ULN
    - (Elevated ALT or AST) and BILI >2×BL and BILI >2×ULN and ALP ≥ 2×ULN
    - (Elevated ALT or AST) and BILI >2×BL and BILI >2×ULN and ALP <2×ULN

Combined elevations post-baseline are based on the peak values at any post-baseline time for a participant.

(Elevated AST or ALT) is defined as:

>3×ULN if ≤ ULN at baseline, or
(>3×BL or >8×ULN) if >ULN at baseline

Potential Hy's Law events are defined as those participants who, depending on their baseline status, fulfill one of the criteria. Further medical review has to be conducted to assess potential confounding factors such as liver metastases, liver function at baseline etc.

In addition, a listing by cohort of the hepatic laboratory values (TBL, ALT, AST and ALP) will be provided with values x.x times above ULN and CTCAE grades flagged. Peak total bilirubin vs peak ALT values will also be graphically presented (eDISH plot).

2.8.4 Other safety data

2.8.4.1 ECG and cardiac imaging data

ECG data will be analyzed based on central laboratory reported results by cohort. The summaries will include all ECG assessments performed no later than 30 days after the last date of study drug. All ECG assessments will be listed, and those collected later than 30 days after study drug discontinuation will be flagged in the listing.

Number and percentage of participants with notable ECG values will be presented by cohort. ECG shift table based on notable values will also be presented by cohort. The followings are the notable ECG values.

- QT and 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 ≤ 60ms
  - 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 value of > 120 ms

In addition, the following analysis will be carried out;

- Descriptive statistical analysis (mean and two-sided 90% confidence interval) by time point of assessment for ΔQTcF (QTcF change from baseline)
- A graphical presentation of ECG mean change from baseline over time will be produced based on time windows.

2.8.4.2 Vital signs

Vital sign assessments are performed in order to characterize basic body function. The following parameters were collected: height (cm), weight (kg), body temperature (°C), pulse rate (beats per minute), systolic and diastolic blood pressure (mmHg) (supine position preferred when ECG is collected).

Data handling

Vital signs collected on treatment will be summarized. Values measured outside of on treatment period will be flagged in the listings.

Data analysis

For analysis of vital signs, the clinically notable vital sign criteria are provided in Table 2-4 below.

Table 2-4 Clinically notable changes in vital signs

Vital sign (unit)	Clinically notable criteria	
	above normal value	**below normal value**
Weight (kg)	increase > 10% from Baseline	decrease > 10% from Baseline
Systolic blood pressure (mmHg)	≥180 and an increase ≥20 from baseline	≤90 and a decrease ≥20 from baseline
Diastolic blood pressure (mmHg)	≥105 and an increase ≥15 from baseline	≤50 and a decrease ≥15 from baseline
Pulse rate (bpm)	≥100 with increase from baseline of ≥25%	≤ 50 with decrease from baseline of ≥25%
Body temperature (ºC)	≥39.1	≤ 35°C

Vital signs shift table based on values classified as notable low, normal, notable high or notable (high and low) at baseline and worst post-baseline will be produced for pulse rate, diastolic BP and systolic BP.

Baseline values (Low/high) are defined as:

- Systolic BP: ≤ 90 mmHg / Systolic BP: ≥ 180 mmHg
- Diastolic BP: ≤ 50 mmHg / Diastolic BP: ≥ 105 mmHg
- Body temperature: ≤ 35°C / Body temperature: ≥ 39.1°C
- Pulse rate: ≤ 50 bpm / Pulse rate: ≥ 100 bpm

The number and percentage of subjects with notable vital sign values (high/low) will be presented by cohort.

The following two listings will be produced by cohort:

- Participants with clinically notable vital sign abnormalities by cohort.

- All vital sign assessments will be listed by participant and vital sign parameter.

In both listings, the clinically notable values will be flagged and also the assessments collected later than 30 days after the last treatment/exposure date will be flagged.

2.8.4.3 ECOG performance status

The ECOG performance status assessment allows participants to be classified as to their functional impairment, the definition of scores in relation to their performance status is provided in Table 2-5, ranging from 0 (most active) to 5 (dead):

Table 2-5 ECOG Performance Scale

Score	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Shift tables of ECOG performance status at baseline to worst or best post-baseline ECOG performance status by score will be provided by cohort using the safety set.

2.9 Pharmacokinetic

Analyses related to pharmacokinetic will not be repeated in the final analysis as no data updates have occurred sine the 12-month update analysis.

2.10 PD and PK/PD analyses

Not applicable.

2.11 Patient-reported outcomes

Patient reported outcomes (PROs) including EORTC QLQ-C30/LC13 EQ-5D-5L and NCCN FACT-Brain Symptom Index (FBrSI) questionnaires will be summarized by cohort. The FAS will be used for analyzing PRO data. The baseline is defined as the last PRO assessment on or prior to randomization.

Descriptive statistics will be used to summarize the individual items and scored sub-scale scores at each scheduled assessment time point by cohort for EORTC QLQ-C30/LC13, EQ-5D-5L and NCCN FACT-Brain Symptom Index (FBrSI).

Scoring of PRO data and methods for handling of missing items or missing assessments will be handled according to the scoring manual and user guide for each respective patient questionnaire (Fayers 2001, Van Reenen 2015). No imputation procedures will be applied for

missing items or missing assessments. Changes from the baseline by cohort at each visit will be ploted for all scales of QLQ-LC13, QLQ-C30, EQ-5D-5L and FBrSI.

PRO Compliance and Completeness

Completion and compliance will be summarized for each scheduled assessment time point by cohort.

Windows for multiple assessments – PRO

Time windows (Table 2-6) are defined for descriptive summary of PRO data by visit and longitudinal data analysis. If more than one assessment is available in the same time window, the assessment closest to the planned date will be considered. If two assessments are obtained with the same time difference compared to the scheduled visit day, the assessment obtained prior to visit will be considered. Data obtained at the end of treatment (EOT) will be classified as other assessment in the corresponding time window. The EOT assessment will be included if collected within 30 days of the last dose intake.

Table 2-6 Time windows for PRO

Time Window	Planned Visit Timing	Time Window Definition
Cycle 1 Day 1/Baseline	Study Day 1	≤Study Days 1
Cycle 3 Day 1 (Week 7)	Study Day 43	Study Days 2 –63
Every 6 weeks thereafter	Scheduled visit day	Scheduled visit day ± 21 days

Study Day 1 = the first day of dosing

Additionally, change from baseline of EORTC QLQ-C30/LC13,EQ-5D-5L, and FBrSI-DRS-P in the domain scores at the time of each assessment will be summarized by cohort. Participants with an evaluable baseline score and at least one evaluable post baseline score during the treatment period will be included in the change from baseline analyses. These PRO scores will also be displayed as mean profiles of change from baseline for each cohort, presented over time using time windows.

Instead of using total score (FBrSI-24 total) which consists of 24 questions (range: 0-96), disease related symptom-physical score (FBrSI-DRS-P) will be used to define the secondary endpoint of change from baseline in symptoms of the brain metastases. FBrSI-DRS-P consists of 12 questions (range:0-48).

2.12 Biomarkers

As a project standard, only biomarker data collected in the clinical database will be analyzed. This study is not adequately powered to assess specific biomarker related hypotheses. The analyses of biomarkers will be reported in the CSR if data are available at the time of clinical database lock and CSR preparation. Otherwise, the results may be reported in a separate report document.

There may be circumstances when a decision is made to stop a sample collection, or not perform or discontinue the analysis of tumor samples due to either practical or strategic reasons (e.g.,

issues related to the quality and or quantity of samples. Under such circumstances, the number of samples may be inadequate to perform a rigorous data analysis and the available data will only be listed.

2.12.1 Outline of the data analysis

The proposed data analysis will be aligned with the secondary biomarker objective of the protocol:

- To evaluate the association between *METex14* mutation status as measured in ctDNA at baseline with ORR, DOR and PFS upon treatment with capmatinib

2.12.2 Data handling principles

Participants with EGFR wild type and ALK-negative rearrangement will be pre-screened for METex14 mutation status by a tumor tissue-based clinical trial assay (CTA) at the Novartis-designated centrallaboratory. Subjects with centrally determined METex14 mutant tumor statuswill be screened for clinical eligibility criteria as described in the original clinical trial protocol. Participants METex14 mutant status will also be tested by the ctDNA at baseline. There is a possibility that those participants whotested positive by CTA, may not be *METex14* positive by ctDNA. The following contingency table (Table 2.7) summaries the concordance and discordance between the tests. Any invalid results from *METex14* ctDNA testing will not be included in the contingency table. The table includes all test results from Cohort 1 and Cohort 2. A list of METex14 mutation result by ctDNA and tumor tissue sample will be summarized.

Table 2-7. Contingency table summarizing the ctDNA Test results and the CTA results at baseline.

		METex14 mutation positive by tumor tissue sample	
METex14 ctDNA results		*METex14* mutation positive	n_1
		METex14 mutation negative	n_2
		Total	N

1. n_1=number of participants with concordance between MET mutation positive by tumor sample and METex14 mutation positive by plasma sample (ctDNA)
2. n_2=number of participants with discordance between MET mutation positive by tumor sample and METex14 mutation negative by plasma sample (ctDNA)
3. N = total number of participants having both test results at baseline

2.12.3 Data analysis principles

2.12.3.1 Analysis set

The FAS will be used for all biomarker analyses. Unless otherwise specified, all statistical analyses of biomarker data will be performed on participants with biomarker data.

2.12.3.2 Basic tables, figures and listings

If the number of participants is considered large enough, the association between *METex14* mutation status and ctDNA will be estimated through concordance and discordance rate. The concordance rate and its exact binomial 95% CI (Clopper and Pearson 1934) will be provided. Concordance will be the proportion (n_1/N) of participant's *METex14* mutant status where tests by ctDNA and tumor tissue simple will have the same results, otherwise discordance.

The evaluation of ORR will be conducted based on BIRC and investigator assessment. ORR will be estimated and the exact binomial 95% CI (Clopper and Pearson 1934) will be provided by *METex14* ctDNA status.

DOR and PFS will be described in tabular and graphical format using Kaplan-Meier methods by ctDNA status (Table 2.7). In the Kaplan-Meier plot the number of participants at risk at certain time points will be shown on the plot. The estimated median (in months) along with 95% CIs, as well as 25th and 75th percentiles will be reported (Brookmeyer and Crowley 1982). In addition, Kaplan-Meier estimated probabilities with corresponding 95% CIs at several time points (including at least 3, 6, 12, and 18 months) will be summarized. These analyses will be performed separately based on BIRC assessment and based on investigator assessment.

2.13 Other Exploratory analyses

CCI [redacted]

2.14 Interim analysis

Interim analyses were conducted independently for both Cohort 1 and Cohort 2 after six cycles of treatment (primary analysis) and after at least 12 months of treatment (12-month update analysis).

3 Sample size calculation

3.1 Primary endpoint(s)

Approximate 35 participants will be treated in this two-cohort study (cohort 1 ~ 15 participants and cohort 2~20 participants). With 15 participants in Cohort 1, the lower bound of exact binomial 95% CI for observed ORR will be at least 38.4% when observed ORR is 66.7%. Similarly, with 20 participants in Cohort 2, the lower bound of exact binomial 95% CI for ORR will be ≥ 19.1% when observed ORR is 40%.

Table 3-1 below shows the results from study [CINC280A2201] which will be used as a reference for sample size calculation.

Table 3-1 Objective response rate (ORR) and 95% lower confidence interval (LCI) (%) in study CINC280A2201

Line	n/N	Point estimate (%)	95% LCI (%)
1L	19/28	67.9	47.6
2/3L	28/69	40.6	28.9

In study [CINC280A2201], 67.9% ORR and 47.6% of its lower limit of 95% CI were observed from 28 participants in the treatment naive cohort. If 10 responders out of 15 participants are observed in this study, cohort 1, it will result ORR of 66.7%. The probability of observing ORR greater than 47.6% is at least 0.89. With 15 participants, Table 3-2 below shows the probability of observing ORR greater than 47.6%.

Table 3-2 Operating characteristics for cohort 1

Sample size	True ORR (%) in Chinese participants	Probability (%) that observed ORR > 47.6% (lower limit in A2201)
15	50	50.0
	55	65.4
	60	78.7
	65	88.7
	70	95.0
	75	98.3

Similarly, in study [CINC280A2201], 40.6% ORR and 28.9% of its lower limit of 95% CI were observed from 69 participants from the pre-treated cohort. If 8 responders out of 20 participants are observed in this study, cohort 2, it will result 40% ORR. The probability of observing ORR greater than 28.9% is at least 0.87. With 20 participants, Table 3-3 below shows the probability of observing ORR greater than 28.9%.

Table 3-3 Operating characteristics for cohort 2

Sample size	True ORR (%) in Chinese participants	Probability (%) that observed ORR > 28.9% (lower limit in A2201)
20	25	38.3
	30	58.4
	35	75.5
	40	87.4
	45	94.5
	50	99.4

4 Change to protocol specified analyses

No change from protocol specified analysis was made.

5 Appendix

5.1 Imputation rules

5.1.1 Study drug

The study drug is INC280/Capmatinib.

5.1.2 AE date imputation

The following missing dates will not be imputed

- Missing AE start dates
- AE start dates missing the year
- Partial/missing AE end dates

AE with uncertain relationship will be considered as treatment-emergent AE.

For other types of missing dates, the rules specified in Tables 5-1 to Table 5-2 will be used.

Table 5-1 AE/treatment date abbreviations

	Day	Month	Year
Partial Adverse Event Start Date	<not used>	AEM	AEY
Treatment Start Date (TRTSTD)	<not used>	TRTM	TRTY

Table 5-2 describes the possible combinations and their associated imputations. The upper text indicates the imputation (NC, A, B, C etc.) and the lower text the relationship of the AE start date to the treatment start date (TRTSTD).

Table 5-2 Imputation algorithm

	AEM MISSING	AEM < TRTM	AEM = TRTM	AEM > TRTM
AEY MISSING	NC Uncertain	NC Uncertain	NC Uncertain	NC Uncertain
AEY < TRTY	(D) Before TRTSTD	(C) Before TRTSTD	(C) Before TRTSTD	(C) Before TRTSTD
AEY = TRTY	(B) Uncertain	(C) Before TRTSTD	(B) Uncertain	(A) After TRTSTD
AEY > TRTY	(E) After TRTSTD	(A) After TRTSTD	(A) After TRTSTD	(A) After TRTSTD

The legend to the above table is shown in Table 5-3.

Table 5-3 Imputation algorithm legend

Relationship	
Before TRTSTD	Indicates AE start date prior to Treatment Start Date
After TRTSTD	Indicates AE start date after Treatment Start Date
Uncertain	Insufficient to determine the relationship of AE start date to Treatment Start Date
Imputation calculation	
NC / Blank	No convention/imputation

Relationship	
(A)	01MONYYYY
(B)	TRTSTD+1
(C)	15MONYYYY
(D)	01JULYYYY
(E)	01JANYYYY

A few examples are shown in Table 5-4.

Table 5-4 Example scenarios

Partial AE start date	Treatment start date	Relationship with TRTSTD	Imputation Calculation	Imputed Date
12MMMYYYY	20OCT2001	Uncertain	NC	<blank>
DDMMM2000	20OCT2001	Before	(D)	01JUL2000
DDMMM2002	20OCT2001	After	(E)	01JAN2002
DDMMM2001	20OCT2001	Uncertain	(B)	21OCT2001
DDSEP2001	20OCT2001	Before	(C)	15SEP2001
DDOCT2001	20OCT2001	Uncertain	(B)	21OCT2001
DDNOV2001	20OCT2001	After	(A)	01NOV2001

5.1.3 Concomitant medication date imputation

The imputation of the start date of concomitant medication will follow the same conventions as for AE dates. Partial concomitant medication end dates will not be imputed.

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 for scenario (B) it will be replaced with "start date of study drug −1".

End date

- Imputed date = min (reference end date, last day of the month), if day is missing
- Imputed date = min (reference end date, 31DEC), if month and day are missing

Reference end date will be the start date of study drug.

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.

Incomplete date of progression –Prior antineoplastic therapy-medication

A missing day is defaulted to the 1st of the month. However, date of progression should be expected to be after start date of prior antineoplastic therapy.

- Imputed date = max (start date of prior antineoplastic therapy, 1st day of the month), if day is missing

5.1.3.2 Post therapies date imputation

Start date

- Imputed date = max (reference start date, first day of the month), if day is missing
- Imputed date = max (reference start date, 01JAN), if day and month are missing

Reference start date will be the last date of study treatment administration + 1.

End date

No imputation.

5.1.3.3 Other imputations

Incomplete date of initial diagnosis of cancer and date of most recent recurrence

A missing day is defaulted to the 15th of the month and a missing month and day is defaulted to 01JAN.

If because of this imputation the chronology of the events is altered then the imputation should be made to the minimum value up to where chronology remains unchanged. E.g. if due to imputation the date of most recent recurrence becomes prior to the initial diagnosis date then it should be set to initial diagnosis date.

Incomplete assessment dates for tumor assessment

All investigation dates (e.g. MRI scan, CT scan) must be completed with day, month and year. If one or more assessment dates are incomplete but other investigation dates are available, the incomplete date(s) are not considered for calculation of the assessment date and assessment date is calculated as the latest of all investigation dates (e.g. MRI scan, CT-scan) if the overall lesion response at that assessment is CR/PR/SD/UNK. Otherwise – if overall response is progression – the assessment date is calculated as the earliest date of all investigation dates at that evaluation number. If all measurement dates have no day recorded, the 1st of the month is used. If the month is not completed, for any of the investigations, the respective assessment will be considered to be at the date which is exactly between the previous and the following assessment. If a previous and following assessment is not available, this assessment will not be used for any calculation.

Incomplete or missing death date

For cases when either day is missing or both month and day are missing for the date of death, the following imputation rules will be implemented:

- If only day is missing, then impute 15th day of the month and year of death.
- If both day and month are missing, then impute 01JUL of the year of death.

5.2 Dose interruptions and changes

This section provides additional details to those included in Section 2.5.2.

All calculations of dose interruptions and dose changes are based on the dose actually taken by the participant.

An interruption is defined as a 0 mg dose taken on one or more days between two non-zero dosing periods. The last zero dose of INC280 followed by permanent discontinuation are not considered as dose interruption.

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

- If an interruption occurs consecutively for at least two days due to the same reason, then it will be counted only once (*example: If the actual dose on days 1-3 is 800 mg and actual dose on days 4-5 is 0 mg and dose interruption on days 4-5 is due to AE, then the total number of dose interruptions is 1*).
- If an interruption occurs consecutively for at least two days due to different reasons, then it will be counted for each reason (*example: If the actual dose on days 1-3 is 800 mg and actual dose on days 4-5 is 0 mg and dose interruption on day 4 is due to AE and dose interruption on day 5 is due to dosing error, then the total number of dose interruptions is 2*).
- If an interruption occurs for more than one day due to the same reason, but the days are not consecutive, i.e. there is at least one dosing day in between, then each dose interruption will be counted as a different occurrence (*example: if the actual dose on days 1, 3 and 5, is 800 mg and actual dose on days 2 and 4 is 0mg, and dose interruptions on day 2 and 4 are both due to dosing error, the total number of dose interruptions is 2*).

A dose change is defined as a change in dosing from one record to the next, however a dose interruption will not be counted as a dose change.

Dose reductions are a subset of dose changes where the total daily dose is lower than the previous non-zero dose.

Case 1: If a participant did not receive the protocol planned dose for any reason, then this is a dose reduction (400 mg, 800 mg).

Patient ID	Start date	End date	Dose	Regimen	Reason	Reduction (derived)	Comments
0001	22/03/2017	25/03/2017	400	ONCE PER DAY	DOSING ERROR	Y	1st administration different from protocol planned dose (800 mg)
	26/03/2017	26/05/2017	800	2 TIMES PER DAY			

Case 2: If, due to a dosing error, a participant receives higher than protocol planned dose and moves down to the planned dose then this is not a dose reduction (800 mg, 1000 mg, 800 mg); However if the change is directly from a higher than planned dose down to a lower than protocol planned dose, then this is a dose reduction (e.g. In the sequence, 800 mg, 1000 mg, 400 mg, is a dose reduction).

Patient ID	Start date	End date	Dose	Regimen	Reason	Reduction (derived)	Comments
0002	22/03/2017	21/05/2017	800	2 TIMES PER DAY			
	22/05/2017	23/05/2017	0		ADVERSE EVENT		

Patient ID	Start date	End date	Dose	Regimen	Reason	Reduction (derived)	Comments
	24/05/2017	01/08/2017	600	2 TIMES PER DAY	ADVERSE EVENT	Y	
	02/08/2017	02/08/2017	700	2 TIMES PER DAY	DOSING ERROR		
	03/08/2017	05/08/2017	800	2 TIMES PER DAY			
	06/08/2017	06/08/2017	**1000**	**2 TIMES PER DAY**	**DOSING ERROR**		
	07/08/2017	12/09/2017	**800**	**2 TIMES PER DAY**		**N**	moves down to the dose administered just before dosing error
0003	22/03/2017	21/05/2017	800	2 TIMES PER DAY			
	22/05/2017	23/05/2017	0		ADVERSE EVENT		
	24/05/2017	01/08/2017	600	2 TIMES PER DAY	ADVERSE EVENT	Y	
	02/08/2017	02/08/2017	700	2 TIMES PER DAY	DOSING ERROR		
	03/08/2017	05/08/2017	800	2 TIMES PER DAY			
	06/08/2017	06/08/2017	**1000**	**2 TIMES PER DAY**	**DOSING ERROR**		
	07/08/2017	12/09/2017	**600**	**2 TIMES PER DAY**		**Y**	moves down to a lower dose administered just before dosing error

Case 3: If due to interruption, a participant receives half of the dose during 1 day and followed by an interruption (due to the same reason) then this is not a dose reduction (for ex: 800 mg 2 times per day from 27-Dec-2016 to 14-Jan-2018, and 400 mg once per day on 15-Jan-2018 and then interruption 16-Jan-2018 to 22-Jan-2018). After interruption, dose reduction will be determined using the dose received on a day without interruption (for ex: 600 mg vs 800 mg ignoring 400 mg on 15-Jan given it is related to the interruption).

Patient ID	Start date	End date	Dose	Regimen	Reason	Reduction (derived)	Comments
0004	27/12/2017	14/01/2018	800	2 TIMES PER DAY			
	15/01/2018	15/01/2018	**400**	**ONCE PER DAY**	**ADVERSE EVENT**	**N**	½ dose for 1 day same reason than interruption Interruption started on 15-Jan
	16/01/2018	22/01/2018	0		**ADVERSE EVENT**		
	23/01/2018	07/02/2018	600	2 TIMES PER DAY	ADVERSE EVENT	**Y**	Dose reduction from 800 mg to 600 mg [400 mg on 15Jan ignored for reduction determination as part of the interruption]
	08/02/2018	19/02/2018	0		ADVERSE EVENT		

Patient ID	Start date	End date	Dose	Regimen	Reason	Reduction (derived)	Comments
0005	25/04/2016	22/05/2016	800	2 TIMES PER DAY			
	23/05/2016	23/05/2016	400	ONCE PER DAY	ADVERSE EVENT	N	½ dose for 1 day same reason than interruption Interruption started on 23-May
	24/05/2016	25/05/2016	0		ADVERSE EVENT		
	26/05/2016	26/05/2016	400	ONCE PER DAY	ADVERSE EVENT	Y	Dose reduction from 800 mg to 400 mg [400 mg on 23May ignored for reduction determination as part of the interruption]
	27/05/2016	05/06/2016	800	2 TIMES PER DAY			
	06/06/2016	06/06/2016	400	ONCE PER DAY	DOSING ERROR	Y	
	07/06/2016	01/08/2016	800	2 TIMES PER DAY			
	02/08/2016	02/08/2016	400	**ONCE PER DAY**	**DOSING ERROR**	**Y**	½ dose for 1 day different reason than interruption
	03/08/2016	07/08/2016	0		**ADVERSE EVENT**		

Case 4: If due to permanent discontinuation, a pa receives half of the dose the last day of treatment then this is not a dose reduction (for ex: 800 mg 2 times per day from 30-May-2016 to 03-Oct-2016, and 400 mg once per day on 04-Oct-2016). This rule is applied for any dose levels (for ex: 600 mg 2 times per day from 15-Dec-2017 to 20-Dec-2017, and 300 mg once per day on 04-Oct-2016).

Patient ID	Start date	End date	Dose	Regimen	Reason	Permanently discontinuation	Reduction (derived)
0006	30/05/2016	03/10/2016	800	2 TIMES PER DAY			
	04/10/2016	04/10/2016	400	ONCE PER DAY	ADVERSE EVENT	Y	N

5.3 Implementation of RECIST guidelines

Disease progression

PD should only be assigned if it is confirmed by an objective assessment method as per RECIST 1.1 (e.g. radiologic scan, histology for bronchoscopy, photos for skin lesions). If a new lesion is detected using an objective assessment method other than radiologic scan, it should be entered on the 'New lesion' RECIST eCRF with appropriate method (or method= 'Other').

In particular, discontinuation due to disease progression or death due to progressive disease, without supporting objective evidence (as defined above), will not be considered as PD in the determination of BOR, the derivation of any efficacy endpoint or efficacy analysis.

Change in imaging modality

Per RECIST 1.1, a change in methodology can be defined as either a change in contrast use (e.g. keeping the same technique, like CT, but switching from with to without contrast use or vice-versa, regardless of the justification for the change) or a change in technique (e.g. from CT to MRI, or vice-versa), or a change in any other imaging modality. A change from conventional to spiral CT and vice versa while keeping same contrast use (e.g. switching from spiral CT with contrast to CT with contrast) is not considered a change in imaging modality. A change in methodology will result by default in a UNK (unknown) overall lesion response assessment. However, a response assessment other than the Novartis calculated UNK response may be accepted from the investigator or BIRC if a definitive response assessment can be justified based on the available information. Potential discrepancies between the modality used and overall lesion response reported by the investigator (e.g. change in modality but investigator assessment of response is different from UNK) will be queried during the data validation process.

Determination of missing adequate tumor assessments

For the computation of ORR, participants without any radiological assessment after the start date of study drug will be counted as failure.

Partial or complete responses reported prior to any additional anticancer therapy will be considered for ORR computation irrespective of the number of missed assessments before response. In this section, the 'missing adequate assessment' is defined as assessment not done or assessment with overall lesion response equal to UNK. For the sake of simplicity, the 'missing adequate assessment' will also be referred as 'missing assessment'.

The PFS censoring and event date options depend on the presence and the number of missing tumor assessments. For example, an event occurring after two or more missing assessments is censored in the analysis of PFS at the last adequate tumor assessment before the event date.

An exact rule to determine whether there is none, one or two missing assessments is therefore needed. This rule will be based on the distance between the last adequate tumor assessment date and the event date.

If the distance is larger than threshold D_1 or D_2 then the analysis will assume one or two missing assessments, respectively. The threshold D_1 will be defined as the protocol specified interval between the tumor assessments plus the protocol allowed window around the assessments. Similarly, the threshold D_2 is defined as two times the protocol specified interval between the tumor assessments plus the protocol allowed window around the assessments. In this study, the protocol defined schedule of tumor assessment is every 6 weeks and each assessment is expected to be performed at the scheduled time point plus or minus 1 week, i.e. the window is 2 weeks, then any distance larger than $D_1 = 6+2 = 8$ weeks means one missing assessment and any distance larger than $D_2 = (2*6) + 2 = 14$ weeks means two missing assessments.

The same definition of D_2 will be used to determine the PFS censoring reason.

Possible censoring reasons for PFS are:

1: Ongoing without event

2: Lost to follow-up

3: Withdrew consent

4: Adequate assessment no longer available

5: New cancer therapy added

6: Event after >=2 missing tumor assessments

PFS censoring reason is then derived by the following sequence of rules.

- If participant is considered to have a PFS event then PFS censoring reason is set to missing.
- Else if participant has had no baseline assessment then PFS censoring reason = 4.
- Else if participant has a PFS event after two or more missing assessments [If (PFS Event date ≤ Censoring date and (PFS Event date - Date of last adequate tumor assessment (LATA) ≥ D2)] then PFS censoring reason =6:
- Else if participant has no PFS event, and participant is censored at a date after two or more missing assessments ((Censoring date - Date of LATA) ≥ D2) then PFS censoring reason = 4
- Else if censoring date equals the start date of further anti-neoplastic therapy then PFS censoring reason = 5
- Else if censoring date equals date of discontinuation due to consent withdrawal then PFS censoring reason = 3
- Else if censoring date equals date of discontinuation due to loss to follow-up then PFS censoring reason = 2
- Else if the censoring date equal the analysis cut-off date and the time between LATA and the cut-off is greater than D2 days then PFS censoring reason = 4
- Else if the censoring date equal the analysis cut-off date and the time between LATA and the cut-off is less than or equal to D2 days then PFS censoring reason = 1

Where censoring date = minimum (analysis cut-off date, start date of further anti-neoplastic therapy, date of discontinuation due to consent withdrawal, date of discontinuation due to loss to follow-up).

Non-measurable disease at baseline

If a participant without measurable disease is enrolled, the intent-to-treat (ITT) principle requires including these participants in the analyses. Hence, analyses will be based on FAS including participants with either measurable or non-measurable disease. Therefore, a rule needs to be specified on how to handle these cases.

Overall lesion response can be derived for participants without measurable disease at baseline as follows (Table 5-5).

Table 5-5 Overall lesion response at each assessment: participants with non-target disease only

Non-target lesions	New Lesions	Overall lesion response
CR	No	CR
Non-CR/Non-PD[1]	No	Non-CR/non-PD
UNK	No	UNK
PD	Yes or No	PD
Any	Yes	PD

[1] In general, the **non-CR/non-PD response** for these participants is considered equivalent to an SD response in endpoint determination.

Missing baseline tumor assessment

As specified in Section 14 (Appendix II) of the protocol, since the timing of PD cannot be determined for participants with missing baseline tumor assessment, these participants are censored in the PFS analysis at the start date of treatment. This rule, however, only applies to the 'PD component' of the PFS or DOR assessment.

Participants without baseline tumor assessment who die within D_2 distance from start date of treatment will be counted as having an event in the analysis of PFS. All deaths will be counted in the OS analysis regardless of presence or absence of the baseline tumor assessment.

5.4 Patient reported outcomes: EORTC QLQ-C30/LC13, EQ-5D-5L and NCCN FACT-Brain Symptom Index (FBrSI)

The text below gives more detailed instructions and rules needed for programming of the analyses described in Section 2.11.

EORTC QLQ-C30 scale scores will be generated by first obtaining the raw scores adding up the item responses on the questions which make up each domain and then applying the linear transformation to the raw scores in accordance with the respective scoring manual provided by the developers (Fayers 2001). Scores in each scale will be generated if at least half of the items comprising the scale have been answered. For single item scales with missing responses and scales where less than half of the items have not been answered, scale scores will be set to missing.

The scoring approach for the QLQ-LC13 is identical in principle to that for the symptom scales/single items of the QLQ-C30. The dyspnea scale of the QLQ-LC13 is the only multi item scale (all others are single item scales) and should only be used if all items comprising the scale have been answered.

The number of participants filling the PRO questionnaires and the number of participants missing PRO assessments out of those eligible to have PRO assessments will be summarized for scheduled assessment time points. The following categories will be used to describe whether the questionnaire was completed at a specific time point:

- yes, fully completed
- yes, partially completed

- no, participant missed scheduled assessment visit
- no, participant refused due to poor health
- no, participant refused (unrelated to health)
- no, study staff felt participant was too ill
- no, questionnaire not available in appropriate language
- no, institutional error
- no, other

EQ-5D-5L (Van Reenen M et al., 2019) consists of 5 questions (5D) with possible choices to answer of any question is 5 (5L). Each participant will be asked about mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The lower the score is the better the outcome for the participant.

NCCN Brain Symptom Index-24 (FBrSI-24) [Lai JS et al., 2014] consists of twenty-four questions. All questions are in 5-point likert scale (0-4) of which some of them are in positive direction and some of them are negative direction. All scores will be converted to positive direction for the statistical analysis and interpretation of the results, following the NFBrSI-SRS-P guidelines in section 7.1.1. Higher score indicates better outcome.
After converting each item score in positive direction, the following formula will be used to get the final score for each participant:

$$FBrSI - 24\ score = \frac{sum\ of\ individual\ item\ scores \times 24}{Number\ of\ item\ answered}$$

FBrSI-DRS-P (Disease Related Symptom-Physical) consists of 12 questions (range:0-48). All questions are in 5-point likert scale (0-4). All scores will be converted to positive direction for statistical analysis and interpretation. Higher score indicates better outcome. Only on-treatment period will be considered.

After converting each item score in positive direction, the following formula will be used to get the final score for each participant:

$$FBrSI - DRS - P = \frac{sum\ of\ individual\ item\ scores \times 12}{Number\ of\ item\ answered}$$

5.5 Adverse events data

5.5.1 Coding of AEs

Adverse events are coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

5.5.2 Grading of AEs

AEs will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5 or higher.

The CTCAE represents a comprehensive grading system for reporting the acute and late effects of cancer treatments. CTCAE version 5 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).

If CTCAE grading does not exist for an adverse event, grades 1 – 5 corresponding to the severity of mild, moderate, severe, life-threatening, and death will be used.

5.6 Laboratory parameters derivations

This section provides further detail on the analysis of laboratory parameters that will be listed and summarized as described in Section 2.8.3.

5.6.1 Hematology

Hematologic tests include: Hemoglobin, platelets, white blood cells (WBC), red blood cells (RBC), differential (basophils, eosinophils, lymphocytes, and monocytes, neutrophils (% or absolute)

The following rules will be applied to derive the WBC differential counts when only percentages are available (this is mainly for neutrophils and lymphocytes, because CTC grading is based on the absolute counts).

The method to convert the value is straightforward: for each participant, the original lab value (%) is divided by 100 and multiplied by WBC count e.g. for neutrophils (NEU):

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

In order to derive the corresponding absolute normal range, the rule to be applied depends on the availability of the % range and the absolute range for the differential:

- If % absolute range NOT missing (% range is or isn't missing), then use the absolute range provided by the site
- If % range NOT missing and absolute range missing, then the % normal limits (i.e. LLN and ULN) are divided by 100 and multiplied by the corresponding normal limits of WBC count, e.g. for neutrophils NEU):

  LLN for NEU count = (LLN for WBC count) * (LLN for NEU%value /100)

  ULN for NEU count = (ULN for WBC count) *(ULN for NEU%value/100)

5.6.2 Biochemistry

The following calculation will be applied for corrected calcium in SI unit (if not available in the Lab database):

Corrected calcium (mmol/L) =measured total Ca (mmol/L) +0.02 (40-serum albumin[g/L]), where 40 represents the average albumin level in g/L.

Time windows will be defined for trends of labs over time.

Table 5-6 Time windows for Labs

Time Window	Planned Visit Timing	Time Window Definition
Baseline	On or before Study Day 1	≤ Study Day 1
Cycle 1 Day 15 (Week 3)	Study Day 15	Study Days 2 – 18
Cycle 2 Day 1 (Week 4)	Study Day 22	Study Days 19 – 32
Cycle 3 Day 1 (Week 7)	Study Day 43	Study Days 33 – 53
Cycle 4 Day 1 (Week 10)	Study Day 64	Study Days 54 – 74
Cycle 5 Day 1 (Week 13)	Study Day 85	Study Days 75 – 95
Cycle 6 Day 1 (Week 16)	Study Day 106	Study Days 96 – 116
Cycle 7 Day 1 (Week 19)	Study Day 127	Study Days 117 – 137
Each and every cycle thereafter until EOT	Scheduled visit day (+ 21 days from previous cycle)	Scheduled visit day ± 10 days centered around the planned assessment

Study Day 1 = the first day of dosing

5.7 Statistical models

5.7.1 Primary endpoint analysis

The estimate of the response rates (e.g., ORR,) will be summarized in terms of percentage rates with 95% CIs. An exact binomial confidence interval (implemented using SAS procedure FREQ with EXACT statement for one-way tables) will be calculated (Clopper and Pearson 1934).

SAS procedure FREQ will be used to estimate the proportion of responders (binary outcome = 1 or "Yes"), along with the associated 95% (=100 × (1 – *two-sided alpha level*)) two-sided exact binomial CI. These estimates are obtained as follows:

```
proc freq data = dataset;
      table binary event /
            binomial(
```

```
                level = "Yes")
          alpha = two-sided alpha level;
    exact binomial;
```

When there are no responders, SAS does not produce a CI by default. To obtain a CI in this situation, PROC FREQ is used as specified above except changing **level**="No". From the results of this modified procedure, the values in percent of the LCL and UCL of a 0% response rate are calculated as follows:

$$LCL_{LEVEL="Yes"}\ (\%) = 100\% - UCL_{LEVEL="No"}\ (\%)$$

$$UCL_{LEVEL="Yes"}\ (\%) = 100\% - LCL_{LEVEL="No"}\ (\%)$$

6 Reference

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7 Appendix

7.1 NCCN/FACT-BrSI Scoring Guidelines

FBrSI-DRS-P Scoring Guidelines

Instructions:* 1. Record answers in "item response" column. If missing, mark with an X

2. Perform reversals as indicated, and sum individual items to obtain a score.

3. Multiply the sum of the item scores by the number of items in the subscale, then divide by the number of items answered. This produces the subscale score.

4. The higher the score, the better the QOL.

Subscale	Item Code	Reverse item?		Item response	Item Score
Disease related Symptom - physical (FBrSI-DRS-P)	An10	4	-	_____	=_____
	Ar21	4	-	_____	=_____
	Br2	4	-	_____	=_____
	Br14	4	-	_____	=_____
Score range: 0-48	Br20	4	-	_____	=_____
	C2	4	-	_____	=_____
	GP3	4	-	_____	=_____
	Br9	4	-	_____	=_____
	GF5	0	+	_____	=_____
	Br1	0	+	_____	=_____
	Br3	0	+	_____	=_____
	Br8	0	+	_____	=_____

Sum individual item scores: _____

Multiply by 12: _____

Divide by number of items answered: _____ ***=FBrSI-DRS-P subscale score***

NOVARTIS

Clinical Development

INC280/Capmatinib/Tabrecta®

CINC280A2204/ NCT04677595

A phase II, multicenter, two-cohort study of oral *MET* inhibitor capmatinib in Chinese adult patients with EGFR wild-type (wt), ALK rearrangement negative, *MET* exon 14 skipping mutations, advanced non-small cell lung cancer (NSCLC) who are treatment naive or failed one or two prior lines of systemic therapy

Statistical Analysis Plan (SAP) Amendment 1

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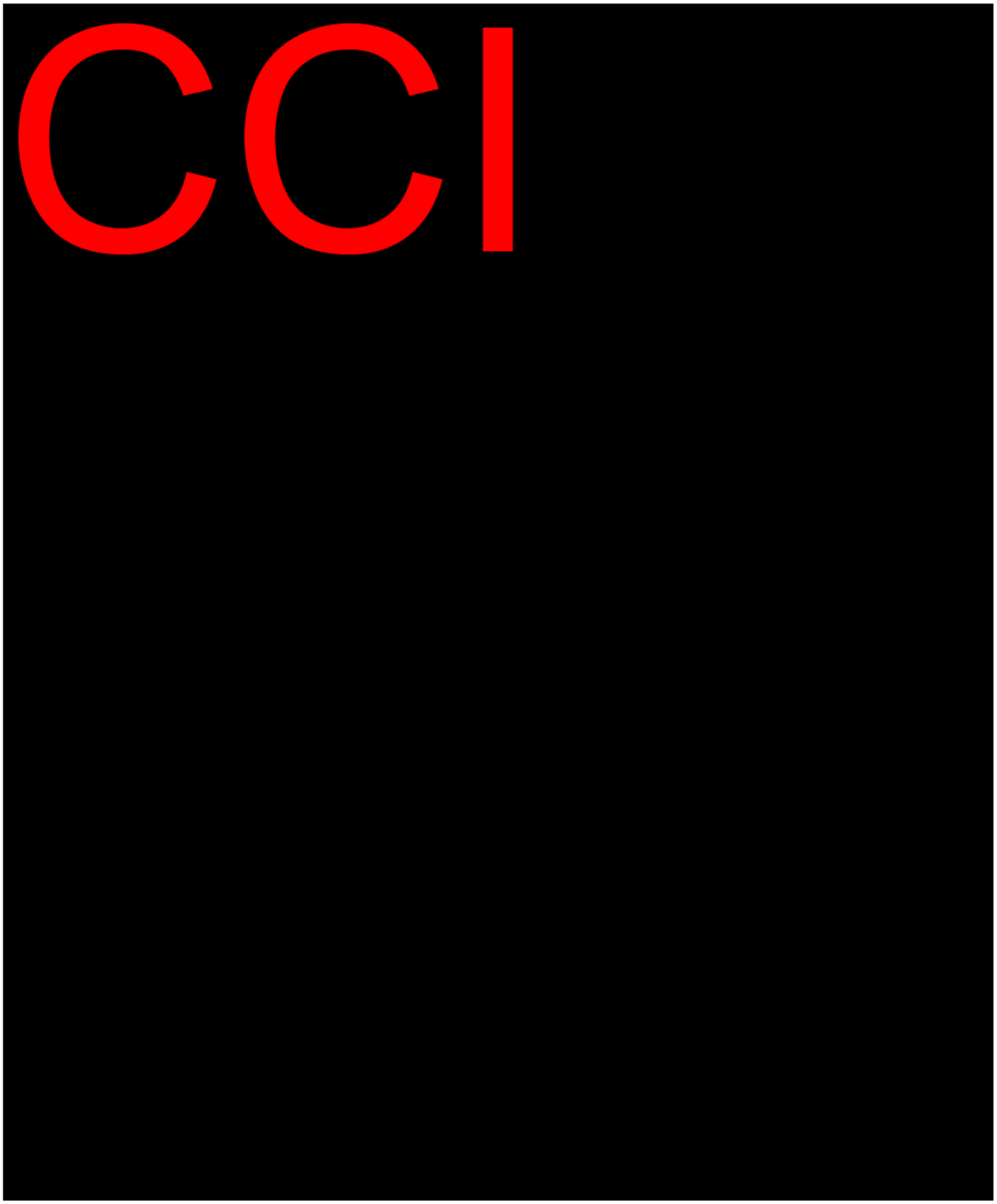


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List of abbreviations

AE	Adverse Event
AESI	Adverse Event of Special Interest
ALP	Alkaline Phosphatase
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/GPT
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
b.i.d.	bis in die/twice a day
TBILI	Total Bilirubin
BIRC	Blinded Independent Review Committee
BOIR	Best Overall Intracranial Response
BOR	Best Overall Response
CI	Confidence Interval
CNS	Central Nervous System
CR	Complete Response
CT	Computed Tomography
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating Tumor DNA
CV	Coefficient of variation
DCR	Disease Control Rate
DNA	Deoxyribonucleic Acid
DOIR	Duration of Intracranial Response
DOR	Duration of Response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EGFR	Epidermal Growth Factor Receptor; also known as ErbB1
EORTC	European Organization for Research and Treatment of Cancer
EOT	End of Treatment
EQ-5D-5L	EuroQoL-5 Dimension-5 Level
FAS	Full Analysis Set
FDA	Food and Drug Administration
FPFV	First Participant First Visit
HR	Hazard Ratio
HRQoL	Health-Related Quality of Life
ICF	Informed Consent Form
IDCR	Intracranial disease control rate
KM	Kaplan-Meier
LLOQ	Lower Limit of Quantification
LPLV	Last Participant Last Visit
MedDRA	Medical Dictionary for Drug Regulatory Affairs
METex14	MET exon 14 skipping
MRI	Magnetic Resonance Imaging

NSCLC	Non-Small Cell Lung Cancer
OIRR	Overall intracranial response rate
ORR	Overall Response Rate
OS	Overall Survival
PAS	Pharmacokinetic Analysis Set
PD	Progressive Disease
PFS	Progression-Free Survival
PK	Pharmacokinetics
PR	Partial Response
PT	Preferred Term
PRO	Patient-reported Outcomes
Q1	First Quartile (25th Percentile)
Q2	Second Quartile (50th Percentile, Median)
Q3	Third Quartile (75th Percentile)
QoL	Quality of Life
QTcF	Corrected QT interval using Fridericia correction
RANO-BM	Response Assessment in Neuro-Oncology Brain Metastases
RECIST	Response Evaluation Criteria in Solid Tumors

1 Introduction

This statistical analysis plan (SAP) describes the planned analyses for the primary and 2nd (if needed) clinical study report(s) (CSR) of study CINC280A2204, a phase II, multicenter, two-cohort study of oral MET inhibitor capmatinib in Chinese adult participants with EGFR wild-type (wt), ALK rearrangement negative, *MET* exon 14 skipping (METex14) mutations, advanced non-small cell lung cancer (NSCLC) who are treatment naive or failed one or two prior lines of systemic therapy.

Primary CSR will be written on all participant data by cohort when all treated participants in that cohort have completed at least 6 cycles of treatment (18 weeks) unless a participant has discontinued treatment earlier. In case one cohort finishes earlier than the other, the primary CSR may be written based on data from that cohort only. Once the second cohort is complete, another CSR may be written.

The content of this SAP is based on protocol CINC280A2204 amended version 1 (dated 19-Jun-2020). All decisions regarding primary analysis, as defined in the SAP document, have been made prior to database lock of the study data.

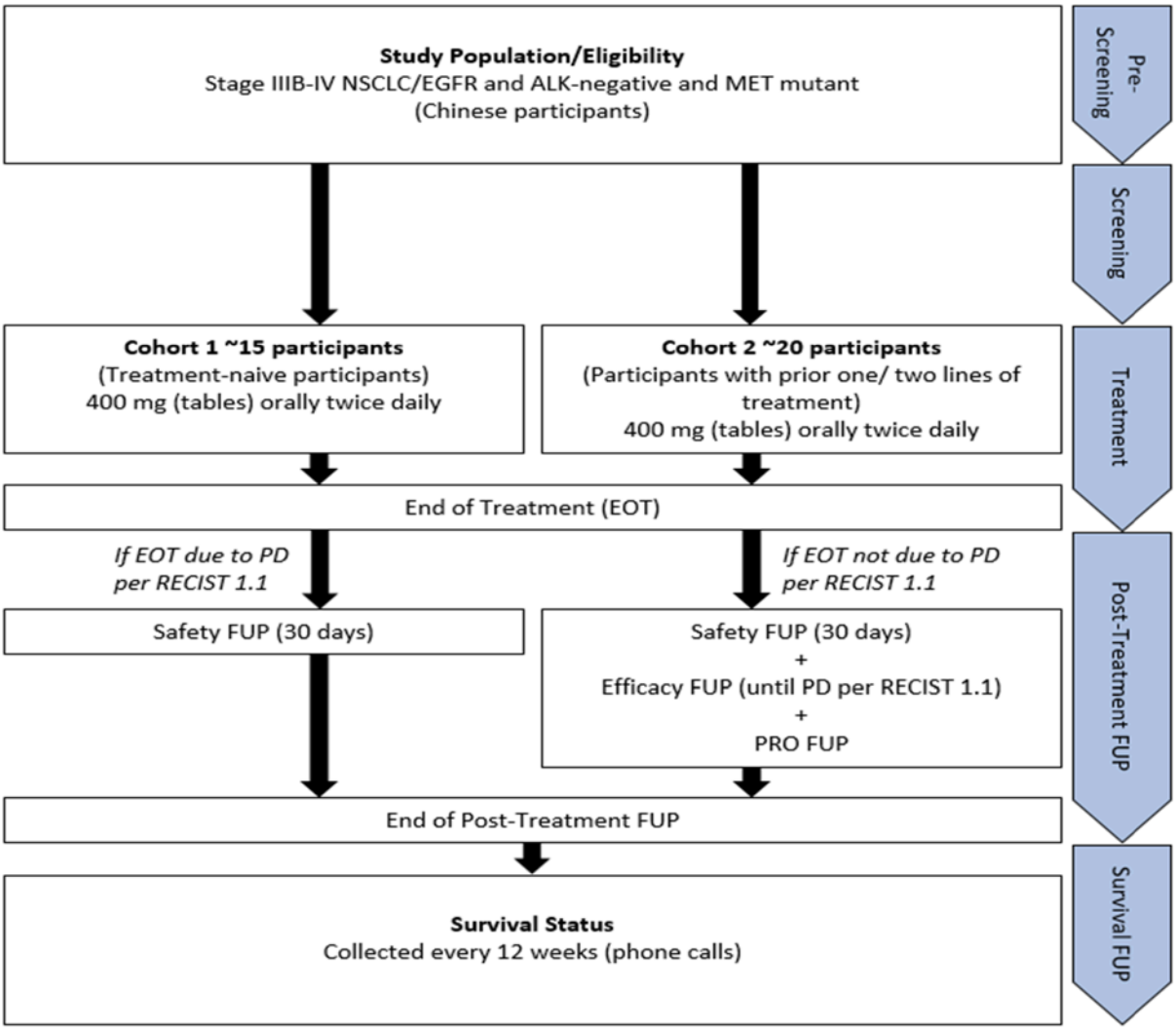
1.1 Study design

This is an open-label, multicenter two-cohort phase II study to evaluate the efficacy and safety of single-agent capmatinib in Chinese participants with EGFR wt (EGFR mutations that predict sensitivity to EGFR therapy, including, but not limited to exon 19 deletions and exon 21 L858R substitution mutations), ALK rearrangement negative, *MET* exon 14 skipping mutated advanced/metastatic NSCLC.

Approximately 35 participants aged 18 or over will be treated in this study in two separate cohorts. Cohort 1 will include approximately 15 treatment naive participants and Cohort 2 approximately 20 participants who failed one or two prior lines of therapy in the advanced stage. Each participant will receive 400 mg capmatinib tablet twice daily (BID).

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

Figure 1.1 Study Design



There is no interim analysis planned and there is no stratification factor for this study.

1.2 Study objectives and endpoints

The following study objectives and endpoints will be assessed in this study.

Table 1-1 Objectives and related endpoints

Objectives	Endpoints
Primary objective	**Endpoints for primary objective**
• To evaluate the antitumor activity of capmatinib, as measured by overall response rate (ORR) by blinded	• ORR, proportion of participants with a best overall response (BOR) defined as complete response or partial response

independent review committee (BIRC) assessment, by cohort	(CR+PR) by BIRC assessment per RECIST 1.1
Secondary objectives	**Endpoints of secondary objectives**
• To evaluate duration of response (DOR) as assessed by BIRC, by cohort	• DOR, calculated as the time from the date of the first documented CR or PR by BIRC per RECIST 1.1 to the first documented progression or death due to any cause for participants with PR or CR
• To evaluate ORR and DOR by investigator assessment, by cohort	• ORR (CR+PR) and DOR per RECIST 1.1 by investigator assessment
• To evaluate time to response (TTR), disease control rate (DCR) and progression-free survival (PFS) by investigator and by BIRC assessment, by cohort	• All calculated per RECIST 1.1, both by BIRC and investigator: – TTR, calculated as the time from first dose of capmatinib to first documented response (CR+PR) for participants with PR or CR – DCR, calculated as the proportion of participants with BOR of CR, PR, or SD – PFS, defined as time from first dose of capmatinib to progression or death due to any cause
• To evaluate overall survival (OS), by cohort	• OS, defined as time from first dose of capmatinib to death due to any cause
• To assess intracranial anti-tumor activity of capmatinib in participants with Central Nervous System (CNS) lesions at baseline by BIRC	• Overall intracranial response rate (OIRR), intracranial disease control rate (IDCR), time to intracranial response (TTIR), duration of intracranial response (DOIR) by BIRC as per RANO-BM criteria
• To evaluate the association between *METex14*mutation status as measured in ctDNA at baseline with capmatinib efficacy	• ORR, DOR and PFS per RECIST 1.1 for participants by *MET* mutation status assessed in ctDNA at baseline, both by BIRC and investigator
• To characterize the pharmacokinetics of capmatinib	• Steady state Ctrough and steady state 0.5-1.5 hour and 3-5 hours post-dose concentrations
• To evaluate capmatinib safety profile	• Incidence of adverse events (AEs) and serious adverse events (SAEs), change in vital signs, laboratory results (hematology, chemistry, and urinalysis) and ECG
• To assess the effect of capmatinib on patient-reported disease-related symptoms, functioning, and health-related quality of life (HRQoL)	• Change from baseline to each visit in European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 function, symptom, and impact

	domains/items; LC13 domain/items; and EuroQoL-5 Dimension-5 Level (EQ-5D-5L) health state utility values and VAS scores.
• To assess the effect of capmatinib on patient-reported symptoms of brain metastases	• Change from baseline to each visit in symptoms of brain metastases, with the NCCN FACT-Brain Symptom Index symptom module (FBrSI)

2 Statistical methods

This section and its subsections will be used to draft CSR Section 9.7 on statistical analyses. The text will be changed to the past tense when imported into the CSR.

2.1 Data analysis general information

The primary analysis will be performed by Novartis statistics and programming team. SAS version 9.4 or later will be used to perform all data analyses and to generate tables, figures and listings.

2.1.1 Data included in the analysis

All treated participants who have completed at least 6 cycles of treatment (18 weeks) or discontinued treatment early will be included in the CSR. In case one cohort finishes earlier than the other, the primary CSR may be written based on data from that cohort only, and in this case there may be two different data cut-off dates. The subsequent CSR will be written based on a second data cut-off date. Any data collected beyond the cut-off date(s) will not be included in the analysis and will not be used for any derivations.

All events with start date before or on the cut-off date and end date after the cut-off date will be reported as 'ongoing'. The same rule will be applied to events starting before or on the cut-off date and not having documented end date. This approach applies, in particular, to adverse event and concomitant medication reports. For these events, the end date will not be imputed and therefore will not appear in the listings.

2.1.2 General analysis conventions

Pooling of centers: Unless specified otherwise, data from all study centers will be pooled for the analyses. Due to expected small number of subjects enrolled at centers, no center effect will be assessed. There is no stratification.

Qualitative data (e.g., gender, race) will be summarized by frequency counts and percentages. Percentages will be calculated using the number of participants in the relevant population or subgroup as the denominator.

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

2.1.3 General definitions

2.1.3.1 Study drug and study treatment

Study drug and study treatment both refer to INC280 (capmatinib) and will be used interchangeably.

2.1.3.2 Date of first administration of study drug

The date of first administration of study drug is defined as the first date when a non-zero dose of study drug was administered and recorded on the Dosage eCRF. For the sake of simplicity, the date of first administration of study drug will also be referred to as start date of study drug.

2.1.3.3 Date of last administration of study drug

The date of last administration of study drug is defined as the last date when a non-zero dose of study drug was administered and recorded on DAR eCRF. This date will also be referred to as last date of study drug.

2.1.3.4 Study day

The study day for all assessments (e.g. tumor assessment, death, disease progression, tumor response, performance status, adverse event onset, laboratory abnormality occurrence, vital sign measurement, dose interruption) will be calculated using the start date of study drug as the origin. For assessments occurring after or on the start date of study drug, study day will be calculated as:

Study Day =Event date - start date of study drug + 1.

The first day of study drug is therefore study day 1.

For any assessment or events such as baseline disease characteristics or medical history (e.g., time since diagnosis of disease) occurring prior to the start of the study drug, study day will be negative and will be calculated as:

Study Day = Event date - start date of study drug.

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

2.1.3.5 Baseline

For efficacy evaluations, the last non-missing assessment, including unscheduled assessments on or before the date of first dose of study treatment is taken as “baseline” value or “baseline” assessment. In the context of baseline definition, the efficacy evaluations also include biomarkers, ECOG performance status and PROs.

For safety evaluations, the last available assessment on or before the date of start of study treatment is taken as “baseline” assessment.

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

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 values are from central and local laboratories, the value from central assessment should be

considered as baseline. If multiple values are from the same local laboratory or collected, then the worst value should be considered as baseline.

2.1.3.6 Last contact date

The last contact date will be derived for participants not known to have died at the analysis cut-off using the last complete date among the following (Refer Table 2-1):

Table 2-1 Last contact date

Source data	Conditions
Last contact date/last date participant was known to be alive from Survival Follow-up page	Participant status is reported to be alive, lost to follow-up or unknown
Start/End dates from further antineoplastic therapy	Non-missing medication/procedure term.
Start/End* dates from drug administration record	Non-missing dose. Doses of 0 are allowed.
End of treatment date from end of treatment page	No condition.
Tumor assessment date	Evaluation is marked as 'done'.
Laboratory/PK collection dates	Sample collection marked as 'done'.
Vital signs 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 participant was seen or contacted on that date. 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 participants in the analysis of overall survival.

2.1.3.7 Time unit

For all derivations, a month will be calculated as (365.25 / 12) = 30.4375 days.

If duration is to be reported in years, duration in days will be divided by 365.25.

If duration is to be reported in months, duration in days will be divided by 30.4375.

If duration is to be reported in weeks, duration in days will be divided by 7.

2.1.3.8 On-treatment period/event and observation period

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

- **Pre-treatment period**: from the day of participant's informed consent to the day before first dose of study drug
- **On-treatment period:**
  - For discontinued participants, from day of first dose of study drug to 30 days after last dose of study drug
  - For ongoing participants, from day of first dose of study drug to the data cut-off date

- **Post-treatment period:** starting at day 31 after last dose of study drug

Safety summaries (tables, figures) and summaries of on-treatment death include only data from the on-treatment period with the exception of baseline data which will also be summarized where appropriate (e.g. change from baseline summaries). In addition, a separate summary for death including on treatment and post treatment deaths will be provided. In particular, summary tables for adverse events (AEs) will summarize only on-treatment events, with a start date during the on-treatment period (***treatment-emergent*** AEs).

All data, regardless of observation period, will be listed and assessments collected in the post-treatment period will be flagged in all the listings.

2.2 Analysis sets

2.2.1 Full analysis set (FAS)

The full analysis set (FAS) comprises all participants to whom study treatment has been assigned and who received at least one dose of capmatinib. Unless otherwise specified, all efficacy analyses will be performed using FAS.

2.2.2 Full analysis set – brain metastases (FAS-BM)

The full analysis set - brain metastases (FAS-BM) comprises all participants in the FAS who have measurable and/or non-measurable brain metastases at baseline.

2.2.1 Evaluable set

The evaluable set comprises all participants in FAS who have at least one post-baseline tumor assessment after treatment.

2.2.2 Safety set

The Safety Set includes all participants who received at least one dose of capmatinib. Unless otherwise specified, all safety data will be analyzed by Safety Set.

2.2.3 Pharmacokinetics analysis set

The Pharmacokinetic Analysis Set (PAS) consists of all participants who received at least one planned dose of study drug INC280 and provide at least one evaluable pharmacokinetic (PK) concentration.

A PK concentration is considered to be evaluable if:

- for PK samples taken on or after Cycle 2 Day 1, the patient took study drug according to the originally assigned dose for at least 3 consecutive days without interruption or dose modification prior to the PK sampling day (ensuring steady state is reached), and
- the participant did not vomit within 4 hours following the last dose intake prior to the PK sample draw, and
- for the pre-dose sample on Cycle 2 Day 1 and Cycle 3 Day 1, PK draw occurred between 9 to 15 hours after the last dose intake and the PK draw occurred before the next dose intake

- for post-dose PK samples, PK with concentrations following planned dose

Any PK 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.

2.2.4 Subgroup of interest

Due to small sample size in each cohort, no formal subgroup analyses are planned. If any subgroup analyses will be needed for further exploration, subgroup analyses will be performed separately and separate analysis plan will be developed.

2.3 Participants disposition, demographics and other baseline characteristics

2.3.1 Participants disposition

The FAS will be used for the subject disposition summary tables by cohort. The FAS will be used for the listings by cohort.

The following will be tabulated:

- Number (%) of participants who are still on-treatment (based on "Treatment disposition")
- Number (%) of participants who discontinued treatment (based on "Treatment disposition" and "Participant status")
- Number (%) of participants who entered post-treatment efficacy follow-up (based on "Post-treatment follow-up disposition" and "Treatment disposition")
- Number (%) of participants who entered survival follow-up (based on completion of 'Subject Status' and "Post-treatment follow-up disposition")
- Number (%) of participants who discontinued from study (based on completion of 'Study Phase Disposition' page with date of discontinuation and discontinuation reasons entered under 'Subject Status' and 'Will subject continue into the next phase of the trial' is 'No' for participants who discontinued from the post-treatment efficacy follow-up)
- Primary reasons for discontinuation from the post-treatment efficacy follow-up (based on discontinuation reasons entered under 'Subject Status' in the 'Study Phase Disposition' page).

2.3.2 Basic demographic and background data

All demographic and baseline disease characteristics data will be summarized and listed by cohort. Categorical data (e.g. gender, ECOG performance status) will be summarized by frequency count and percentages. Continuous data (e.g. age, weight, height, BMI) will be summarized by descriptive statistics using FAS.

2.3.3 Diagnosis and extent of cancer

Summary statistics will be tabulated for diagnosis and extent of cancer by cohort using FAS. This analysis will include the followings: primary site of cancer, stage at initial diagnosis, stage at time of study entry, time (in months) since most recent relapse/progression, histological grade, predominant histology/cytology, types of lesions (target and non-target lesions) at baseline, number of target lesions at baseline, and disease burden at baseline for target lesion (based on the data collected on the RECIST eCRF page) and other relevant information if collected.

2.3.4 Medical history

Medical history and ongoing conditions, including cancer-related conditions and symptoms will be summarized and listed by cohort using FAS. Separate summaries will be presented for ongoing and historical medical conditions. The summaries will be presented by primary system organ class (SOC) and preferred term (PT). Medical history and current medical conditions are coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The MedDRA version used for reporting will be specified in the CSR and as a footnote in the applicable tables/listings.

2.3.5 Screen failures

Screen failures are participants who have been enrolled and have failed to meet inclusion or exclusion criteria. These participants are not treated with study drug. Frequency counts and percentages will be tabulated for all enrolled participants by cohort as follows:

- Number (%) of participants who completed screening phase (based on the presence of study phase completion date and the 'Next phase entered' is 'Treatment' in the 'Screening Phase Disposition' page);
- Number (%) of participants who discontinued during screening phase (based on the presence of date of discontinuation and discontinuation / "subject status" reason entered and 'Will the participant continue into the next phase of the trial' is 'No' in the 'Screening Phase Disposition' page);
- Reasons for screening phase discontinuation (based on reasons recorded in Screening Phase Disposition' page).

All screen failure participants with reasons for screen failure will be listed by cohort.

2.4 Protocol deviations

The number (%) of subjects in the FAS with any protocol deviation will be tabulated by deviation category (as specified in the edit-check specification) overall and by cohort for the FAS. All protocol deviations will be listed.

The outbreak of the Covid-19 pandemic may neccesiate some changes to the study conduct such that the protocol could not be followed strictly. To understand the effect of the pandemic on the execution and outcome of the study, deviations will be identified and recorded as protocol deviations.

In addition to the pre-defined standard PD terms, Novartis has defined 6 new protocol deviations and the corresponding relationship (health status related vs. site lockdown,

participant concern, etc.) to the COVID-19 pandemic in line with "FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency" (March 2020) and "Guidance on the management of clinical trials during the COVID-19 (coronavirus) pandemic" (April 2020) from EMA as listed below.

- Missing visits
- Changes in procedures and assessments
- Planned visits not done at sites
- Changes in drug supply method
- Treatment not given
- Participant's discontinuation due to COVID-19 situation

The COVID-19 related protocol deviations will be summarized separately by cohort if applicable.

2.5 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

2.5.1 Study treatment / compliance

Study drug and study treatment

Study drug and study treatment both refer to INC280 and will be used interchangeably.

Dose exposure and intensity

Definitions of duration of exposure, cumulative dose, average daily dose, dose intensity (DI), relative dose intensity (RDI), as well as intermediate calculations, include:

- Duration of exposure (days): last date of study drug − first date of study drug + 1 (periods of interruption are not excluded)
- Cumulative dose (mg): total dose of study drug taken by a participant in the study
- Number of dosing days (days): duration of exposure − number of zero dose days
- Average daily dose (mg/day): cumulative dose (mg)/number of dosing days (days)
- DI (mg/day): cumulative dose (mg)/duration of exposure (days)
- PDI (mg/day) planned cumulative dose (mg)
- RDI (%): 100 × [DI (mg/day)/PDI (planned dose (800 mg/day)]

Note: Because the planned INC280 dose is 800 mg/day, or the planned dose intensity (PDI) is 800 mg/day, RDI (%) can be calculated by 100*DI/PDI and simplified as shown above.

Duration of study exposure to study drug, cumulative dose, average daily dose, DI and RDI will be summarized by cohort. In addition, the duration of exposure to study drug will be categorized into time intervals and frequency counts and percentages of participants with exposure in each time interval will be presented.

2.5.2 Dose interruptions or permanent discontinuations

Frequency counts and percentages of participants who have dose changes, reductions or interruptions, and the corresponding reasons, will be summarized by cohort.

An analysis of time to first interruption (in weeks) will be presented based on simple descriptive statistics (not using time-to event methods).

Time to first interruption is the time from date of first administration of study drug to the first date when a zero dose of study drug is recorded on the DAR eCRF, expressed in weeks.

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 and mentioned in multiple entries on consecutive days, then it will be counted as one interruption.

Listings of all doses of the study drug along with dose change and dose interruption reasons will be produced by cohort.

Section 5.2 provides further details on the definition of dose changes and interruptions.

2.5.3 Prior, concomitant and post therapies

2.5.3.1 Prior anti-cancer therapy

The number and percentage of participants who received any prior anti-neoplastic medications, prior anti-neoplastic radiotherapy or prior anti-neoplastic surgery will be summarized by cohort.

Prior anti-neoplastic medications will be summarized by chemotherapy (medication) setting, other therapy (medication) setting, number of prior regimens of anticancer medications and prior anticancer medications. Prior antineoplastic medications will also be summarized by ATC class, and preferred term. The medication therapy type of any combination therapy will be classified based on the following order: immunotherapy, chemotherapy, biologic therapy (other than immunotherapy), targeted therapy. For example, a combination therapy of chemotherapy and immunotherapy will be classified as 'immunotherapy'.

Prior anti-neoplastic medications for therapeutic setting (any line, 1st line, 2nd line) will be summarized by line: single agent chemotherapy, Platinum based chemotherapy, immunotherapy, chemotherapy in combination with immunotherapy.

For radiotherapy, time since last radiotherapy, locations and setting of last therapy will be summarized.

For prior surgery, time since last surgery, procedure and residual disease of last therapy will be summarized.

All the above analyses will be performed separately by cohort.

Prior anti-neoplastic therapy will be listed by cohort in three separate listings:
1. Medications
2. Radiotherapy
3. Surgery

2.5.3.2 Concomitant therapy

Concomitant therapies are defined as any medications (excluding study drug, prior antineoplastic treatments and blood transfusions), surgeries, palliative radiotherapies or procedures (including physical therapy) administered in the study and are recorded in the Prior and Concomitant Medications and the Surgical and Medical Procedures eCRF, respectively.

Concomitant medications will be coded using the WHO Drug Reference Listing (WHO DRL) dictionary that employs the WHO Anatomical Therapeutic Chemical (WHO ATC) classification system. Surgeries or procedures will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology. All summaries will be tabulated using frequency counts and percentages.

Concomitant therapies will be summarized by ATC class, preferred term and cohort. Surgical and medical procedures will be coded using MedDRA and summarized by SOC and preferred term. These summaries will include: 1) medications starting on or after the start of study drug but starting no later than 30 days after last dose of study drug and 2) medications starting prior to the start of study drug but continuing after the start of study drug.

All concomitant therapies will be listed by cohort. Any concomitant therapies starting and ending prior to the start of study drug or starting more than 30 days after the last date of study drug will be flagged in the listings.

2.5.3.3 Antineoplastic therapy after discontinuation of study drug

The FAS will be used for all listings and summaries of antineoplastic therapies initiated after discontinuation of study drug. All summaries will be tabulated using frequency counts and percentages by cohort.

Antineoplastic medications initiated after discontinuation of study drug will be summarized and listed by Anatomical Therapeutic Chemical (ATC) class, preferred term and cohort.

Antineoplastic radiotherapy since discontinuation of study treatment will be summarized and listed by setting and cohort.

Antineoplastic surgery since discontinuation of study treatment will be summarized and listed by SOC and preferred term and cohort.

2.6 Analysis of the primary objective

The primary analysis will be conducted when at least all treated participants completed 6 cycles of treatment (18 weeks) or discontinued early (Refer to protocol section 12.4)

2.6.1 Primary endpoint

The primary objective is to demonstrate the antitumor activity of INC280, as measured by overall response rate (ORR) to INC280 by Blinded Independent Review Committee (BIRC) assessment, by cohort.

2.6.1.1 Primary estimand

The primary scientific question of interest is: What is the effect of capmatinib in inducing radiological response by blinded independent review committee (BIRC) as per response evaluation criteria in solid tumors (RECIST) 1.1 in Chinese participants who are either treatment naive or failed one or two prior lines of systemic therapy with METΔex14 mutation, regardless of study treatment discontinuation and prior to start of new anti-neoplastic therapy by cohort?

The primary estimand will be described by the following five attributes:

1. The **population** is the adult Chinese paticipants with EGFR wild-type(wt), ALK rearrangement negative, MET exon 14 skipping mutations advanced non-small cell lung cancer (NSCLC) who are either treatment naive or failed one or two prior lines of systemic therapy
2. The treatment attribute is the oral dose of Capmatinib 400 mg administered twice daily (BID) i.e. total dose of 800 mg daily
3. The variable is the best overall response (BOR) by cohort defined as the best response recorded from the date of treatment start until disease progression/recurrence (taking as reference for PD, the smallest measurement recorded since the treatment started) based on BIRC per RECIST 1.1. prior to start of any neoantiplastic therapy
4. The **intercurrent events** of interest are
    a. The treatment discontinuation for any reason: tumor assessment data collected irrespectively of treatment discontinuation will be included to derive BOR (treatment strategy)
    b. Start of neoantiplastic therapy: any tumor response after the antineoplastic therapy will be considered as non-responser (composite strategy)
    c. Any public health emergency as declared by local or regional authories i.e. pandemic, epidemic or natural disaster: assessment collected irrespectively of those events will be included to derive BOR (treatment policy strategy)
5. The summary measure is the overall best overall response rate (ORR) and its exact 95% confidence interval (CI) (Clopper and Pearson 1934) will be provided by cohort.

2.6.1.2 Statistical hypothesis, model, and method of analysis

The primary analysis will be performed on the FAS. The primary efficacy endpoint ORR will be estimated and the exact 95% confidence interval (CI) (Clopper and Pearson 1934) will be provided by cohort.

The study is based on estimation of the endpoint and therefore **no statistical hypothesis** test will be performed.

2.6.1.3 Handling of intercurrent events of primary estimand

Tumor assessment data collected irrespective of treatment discontinuation until the start of new anti-cancer therapy will be included to derive BOR.

If any new anti-cancer therapy is taken, any subsequent assessments would be excluded from the BOR determination. In case of any missed visit due to health emergencies as declared by local authorities (pandemic, epidemic or natural disaster) will be included for the BOR calculation.

2.6.1.4 Handling of missing values/censoring/discontinuations

Confirmed PR or CR reported prior to any additional anticancer therapy will be considered as responses in the calculation of the ORR irrespective of the number of missed assessments before response.

Participants with a BOR of 'Unknown' per RECIST 1.1 will be considered as non-responders when estimating ORR.

Participants with no BIRC data will be considered as non-responders when estimating ORR.

Participants who have disease progression and continue to receive study drug after progression will qualify for PD at the time of progression and will be counted as PD in the derivation of ORR and any other efficacy endpoints.

2.6.2 Supportive analyses

ORR by BIRC will be summarized by evaluable sets to support the primary analysis.

2.7 Analysis of secondary objective(s)

2.7.1 Efficacy secondary endpoints

2.7.1.1 Duration of response (DOR)

DOR only applies to participants whose BOR is complete response (CR) or partial response (PR) according to RECIST 1.1 based on tumor response data. The start date is the date of first documented response of CR or PR (i.e. the start date of response, not the date when response was confirmed), and the end date is defined as the date of the first documented progression or death due to any cause. DOR will be assessed as per BIRC review and by investigator assessment for both FAS and evaluable sets.

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

Table 2-2 Outcome and event dates for DOR and PFS analyses

	Situation	Date	Outcome
A	No baseline assessment	Date of first dose of study drug [a]	Censored
B	Progression at or before next scheduled Assessment	Date of progression	Progressed
C1	Progression or death after exactly one missing assessment	Date of progression (or death)	Progressed
C2	Progression or death after two or more missing assessments	Date of last adequate assessment	Censored

	Situation	Date	Outcome
D	No progression	Date of last adequate assessment	Censored
E	Treatment discontinuation due to 'Disease progression' without documented progression, i.e. clinical progression based on investigator claim	N/A	Information ignored. Outcome derived based on radiology data only.
F	New anticancer therapy given	Ignore the new anticancer therapy and follow situations above	As per above situations
G	Deaths due to reason other than deterioration of 'Study indication'	Date of death	Progressed

[a] The rare exception to this is if the participant dies no later than the time of the second scheduled assessment as defined in the protocol in which case this is a PFS event at the date of death

The date of last adequate tumor assessment is the date of the last tumore assessment with overall lesion response of CR, PR, SD, or non-CR/non-PD before an event or a censoring reason occurred. In this case, the last tomor evaluation date at that assessment will be used. Participants without a post-baseline tumor assessment will be censored at the time of the first treatment.

DOR will be described in tabular and graphical format using Kaplan-Meier methods by cohort. In the Kaplan-Meier plot the number of participants at risk at certain time points will be shown on the plot. The estimated median (in months) along with 95% CIs, as well as 25th and 75th percentiles will be reported (Brookmeyer and Crowley 1982). In addition, Kaplan-Meier estimated probabilities with corresponding 95% CIs at several time points (including at least 3, 6, 12, and 18 months) will be summarized. These analyses will be performed separately based on BIRC assessment and based on investigator assessment.

2.7.1.2 ORR by investigator assessment

The evaluation of ORR will be also conducted based on investigator assessment. ORR will be estimated and the exact binomial 95% CI will be provided by cohort. The same process described in section 2.6.1 will be followed to evaluate ORR.

2.7.1.3 Time to response (TTR)

TTR is defined as the time from the date of start of study drug to the first documented response of either complete response (CR) or partial response (PR), which must be subsequently confirmed (although date of initial response is used, not date of confirmation). TTR will be evaluated as per BIRC and also by investigator review and according to RECIST 1.1.

Participants without a confirmed CR or PR will be censored at the study-maximum follow-up time (i.e. first participant first visit (FPFV) to last participant last visit (LPLV)) for participants with a PFS event (i.e. disease progression or death due to any cause), or at the date of the last adequate tumor assessment for participants without a PFS event.

TTR will be summarized in 6-weeks intervals using descriptive statistics by cohort. The distribution of time to response will be estimated using the Kaplan-Meier method and the

median time to response will be presented along with 95% confidence interval only if a sufficient number of responses is observed. Failure curves (ascending Kaplan-Meier curves) will be constructed. These analyses will be performed separately based on BIRC assessment and based on investigator assessment.

2.7.1.4 Disease control rate (DCR)

DCR is defined as the proportion of participants with best overall response of CR, PR, or SD per RECIST 1.1. DCR will be estimated and the binomial exact 95% CI will be provided by cohort. These analyses will be performed separately based on BIRC assessment and based on investigator assessment.

2.7.1.5 Progression-free survival (PFS)

PFS is defined as the time from the start date of study drug to the date of the first radiologically documented PD or death due to any cause.

If a participant has not progressed or is not known to have died at the date of analysis cut-off, PFS will be censored at the date of the last adequate tumor evaluation before the cut-off date. PFS events documented after the initiation of neoantineoplastic therapy will be considered provided tumor assessments continue after initiation of the new cancer therapy. Clinical deterioration will not be considered as a qualifying event for progression. Refer to Table 2-2 for censoring and event date options and outcomes for PFS.

PFS will be described in tabular and graphical format using Kaplan-Meier methods as described for DOR by cohort, including estimated median (in months) with 95% CI, 25th and 75th percentiles and Kaplan-Meier estimated probabilities with corresponding 95% CIs at several time points. Censoring reasons will also be summarized by cohort.

These analyses will be performed separately based on BIRC assessment and based on investigator assessment.

2.7.1.6 Overall survival (OS)

OS is defined as the time from the start date of study drug to the date of death due to any cause. If the participant is alive at the date of the analysis cut-off or lost to follow-up, then OS will be censored at the last contact date prior to data cutoff date (see Section 2.1.3.6) for further details on derivation of last contact date).

OS will be described in tabular and graphical format using Kaplan-Meier methods as described for DOR by cohort, including estimated median (in months) with 95% CI, 25th and 75th percentiles and Kaplan-Meier estimated probabilities with corresponding 95% CIs at several time points. Censoring reasons will also be summarized by cohort.

2.7.1.7 Overall intracranial response rate (OIRR)

OIRR is calculated based on response assessments in the brain for participants having measurable and/or non-measurable brain metastases at baseline. OIRR is the proportion of participants with a confirmed best overall intracranial response (BOIR) of CR or PR from the start of treatment until disease progression /recurrence (taking as reference for PD the smallest

measurements recorded since the treatment started) per RANO-BM criteria as assessed by BIRC review (See Reference)

The BOIR for each participant is determined from the sequence of overall (lesion) responses according to the following rules:

- CR = at least two determinations of CR at least 4 weeks apart before progression where confirmation required or one determination of CR prior to progression where confirmation not required
- PR = at least two determinations of PR or better at least 4 weeks apart before progression (and not qualifying for a CR) where confirmation required or one determination of PR prior to progression where confirmation not required
- SD = at least one SD assessment (or better) > 6 weeks after start of treatment (and not qualifying for CR or PR).
- PD = progression ≤ 12 weeks after start of treatment (and not qualifying for CR, PR or SD).
- Not evaluable (NE) = all other cases (i.e. not qualifying for confirmed CR or PR and without SD after more than 6 weeks or early progression within the first 12 weeks)

While evaluating for the OIRR, the followings will be considered:

- any assessments taken more than 30 days after the last dose of study treatment will not be included in the best overall intracranial response derivation.
- any alternative cancer therapy taken while on study any subsequent assessments would ordinarily be excluded from the best overall intracranial response determination.

OIRR calculated based on the data from the FAS-BM and the corresponding 95% CI based on the exact binomial distribution (Clopper and Pearson 1934) will be presented by cohort.

In case of very limited participants will be experiencing brain metastasis, only listing by cohort will be provided.

2.7.1.8 Intracranial disease control rate (IDCR)

IDCR is calculated based on response assessments in the brain for participants having measurable and/or non-measurable brain metastases at baseline. IDCR is the proportion of participants with a confirmed BOIR of CR or PR or SD (or non-CR/non-PD) per RANO-BM criteria as assessed by BIRC review.

IDCR calculated based on the data from the FAS-BM and the corresponding 95% CI based on the exact binomial distribution (Clopper and Pearson 1934) will be presented by cohort.

In case of very limited participants will be experiencing brain metastasis, only listing by cohort will be provided.

2.7.1.9 Time to intracranial response (TTIR)

TTIR is defined as the time from the date of the start of study treatment to the date of the first documented intracranial response of either CR or PR per RANO-BM criteria as assessed by the

BIRC review, which must be subsequently confirmed (date of initial response is used, not date of confirmation).

All participants in the FAS-BM will be included in TTIR calculations. Participants without a confirmed intracranial CR or PR will be censored at the study-maximum follow-up time (i.e. LPLV−FPFV), for participants with an intracranial PFS event (intracranial progression or death due to any cause), or at the date of the last adequate tumor assessment in brain for participants without an intracranial PFS event.

Median TTIR with corresponding 95% CI, and 25th and 75th percentiles (Brookmeyer and Crowley 1982, Klein and Moeschberger 1997) will be presented. TTIR will be summarized using the KM method, based on data from the FAS-BM. KM estimates for TTIR proportions at specific time points, along with 95% CI (Greenwood's formula, Kalbfleisch and Prentice 2002) will also be provided by cohort.

In case of very limited participants will be experiencing brain metastasis, only listing by cohort will be provided.

2.7.1.10 Duration of intracranial response (DOIR)

DOIR only applies to participants whose confirmed BOIR is CR or PR per RANO-BM criteria as assessed by the BIRC review. DOIR is defined as the time from the date of first documented intracranial response of either CR or PR to the date of the first documented intracranial progression per RANO-BM criteria as assessed by BIRC review or date of death due to any cause.

Participants with a confirmed intracranial CR or PR will be censored if they have disease progression in organs other than brain and have no scans in brain after that. Participants will also be censored for death due to other causes. The censoring date will be the date of the last adequate tumor assessment in brain.

Table 2-3 Outcome and event dates for DOIR

	Situation	Date	Outcome
A	No baseline assessment in the brain	Date of first dose of study drug [a]	Censored
B	Intracranial progression at or before next scheduled assessment	Date of intracranial progression	Progressed
C1	Intracranial progression or death after exactly one missing assessment	Date of intracranial progression (or death)	Progressed
C2	Intracranial progression or death after two or more missing assessments	Date of last adequate tumor assessment in the brain	Censored
D	No intracranial progression including disease progression (RECIST) in organs other than brain and have no scans in brain after that	Date of last adequate assessment in the brain	Censored
E	Treatment discontinuation due to 'Disease progression' without documented progression, i.e. clinical progression	Date of last adequate tumor assessment in the brain	Censored

	Situation	Date	Outcome
	based on investigator claim but no intracranial progression and no brain scan after that		
F	New anticancer therapy given	Ignore the new anticancer therapy and follow situations above	As per above situations
G	Deaths due to reason any cause	Date of death	Progressed

The rare exception to this is if the participant dies no later than the time of the second scheduled assessment as defined in the protocol in which case this is a PFS event at the date of death

DOIR will be summarized using the KM method. Median DOIR, with corresponding 95% CI, and 25th and 75th percentiles (Brookmeyer and Crowley 1982, Klein and Moeschberger 1997) will be presented. KM estimates for DOIR proportions at specific time points, along with 95% CI (Greenwood's formula, Kalbfleisch and Prentice 2002) will also be provided by cohort.

In case of very limited participants will be experiencing brain metastasis, only listing by cohort will be provided.

Sensitivity analysis

Sensitivity analysis will be performed for DOR and PFS. In the sensitivity analysis of DOR and PFS, for subjects who receive antineoplastic therapy, the event will be censored at the last tumor assessment prior to the antineoplastic therapy. Every other event/censoring criteria on Table 2.2 will remain the same.

2.8 Safety analyses

For all safety analyses, the safety set will be used. All listings and tables will be presented by cohort.

2.8.1 Adverse events (AEs)

AEs will be coded using MedDRA using the latest version available prior to clinical database lock and will be graded using Common Terminology Criteria for Adverse Events (CTCAE) version 5. If CTCAE grading does not exist for an AE, grades 1, 2, 3, 4, and 5 corresponding to the severity of mild, moderate, severe, life-threatening, and death, respectively, will be used.

All AE summaries will be summarized (frequency counts and percentages) by system organ class and/or preferred term, and maximum severity grades, except where otherwise noted. A participant with multiple CTC grades for an AE will be summarized under the maximum CTC grade recorded for the event.

The following AE summaries will be produced:

- AEs regardless of study drug relationship
- AEs suspected to be study drug related
- SAEs regardless of study drug relationship
- SAEs suspected to be study drug related

- AEs leading to permanent study drug discontinuation of study drug regardless of study drug relationship
- AEs leading to permanent study drug discontinuation of study drug suspected to be study drug related
- AEs requiring dose adjustment and/or study drug interruption regardless of study drug relationship
- AEs requiring dose adjustment and/or study drug interruption suspected to be study drug related
- AEs requiring significant additional therapy regardless of study drug relationship
- AEs requiring significant additional therapy suspected to be study drug related
- AEs excluding SAEs

In addition, a summary of serious adverse events with number of occurrences will be produced (an occurrence is defined as >1 day between start and prior end date of record of same preferred term).

2.8.1.1 Adverse events of special interest / grouping of AEs

An adverse event of special interest is a grouping of adverse events that are of scientific and medical concern specific to compound INC280. These groupings are defined using MedDRA terms, SMQs (standardized MedDRA queries), HLGTs (high level group terms), HLT (high level terms) and PTs (preferred terms). Customized SMQs (Novartis MedDRA queries, NMQ) may also be used. An 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.

All AESI definitions or AE grouping are specified in the electronic Case Retrieval Strategy (eCRS), in which they are identified by the flag "SP". Additional AESI may be reported if there are any updates to the eCRS at the time of the analyses.

Adverse events of special interest (AESIs) INC280 are:

- Hepatotoxicity
- Renal dysfunction
- ILD/Pneumonitis
- Central nervous system toxicity
- Pancreatitis
- Phototoxicity
- Teratogenicity
- Drug-drug interactions with strong CYP3A4 inducers
- QTc interval prolongation

For each specified AESI, number and percentage of participants with at least one event of the AESI occurring during on treatment period will be summarized.

Summaries of these AESIs will be provided by cohort, (specifying grade, SAE, relationship, leading to permanent treatment discontinuation, leading to dose adjustment/interruption, death, etc.).

2.8.2 Deaths

Separate summaries for on-treatment and all deaths will be produced by cohort, system organ class and preferred term.

All deaths will be listed, post treatment deaths will be flagged. A separate listing of deaths prior to starting treatment will be provided for all screened participants.

2.8.3 Laboratory data

Laboratory data assessments will be performed locally. The summaries will include all laboratory assessments collected no later than 30 days after study drug discontinuation. All laboratory assessments will be listed and those collected later than 30 days after study drug discontinuation will be flagged in the listings.

Laboratory data will be classified (by Novartis Oncology Statistical Programming) into CTC grades according to the NCI CTCAE v5.0. For all reports, CTC grade is always obtained on the converted measurement in SI unit. The CTC grade 0 will be assigned as below in different scenarios:

- For lab parameters defined by criteria based on normal range only, a severity grade of 0 will be assigned when the value is within normal limits.
- For lab parameters whose grade is defined by criteria based on normal range and absolute values (e.g. platelet count decrease). A severity grade of 0 will be assigned when the value is within normal limits.
- For lab parameters whose grade is defined by criteria based on normal range and the change from baseline value, with no other associated clinical criteria such as concomitant medication (e.g. creatinine increased) the following will be applied. For the baseline grading and for the grading of post-baseline lab values with missing baseline grading, the grade will be derived using the criteria based only on the normal range as per NCI CTCAE version v5.0. A severity grade of 0 will be assigned when the post-baseline value is $\leq$ ULN (for hyper) or $\geq$ LLN (for hypo).

Parameters for which a grading does not exist will be classified into low/normal/high group by means of laboratory normal ranges.

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

- Shift tables using CTC grades to compare baseline to the worst post-baseline value for laboratory parameters with CTC grades
- Shift tables using low, normal, high (as well as low and high combined) classifications to compare baseline to the worst post-baseline value for laboratory parameters where CTC grades are not defined.
- New or worsened abnormalities for laboratory parameters based on CTC grade

- Trends of renal function parameters (creatinine, urea) over time (baseline and selected on-treatment time-points) will be displayed via boxplots based on time windows and corresponding tables displaying the statistics used for the box plots by the selected time points.

The following lab parameters will be summarized by cohort:

- Hematology: absolute lymphocytes, absolute neutrophils, hemoglobin (anemia), WBC, platelet counts, absolute basophils, absolute eosinophils, absolute monocytes, hematocrit
- Biochemistry: alkaline phosphatase (ALP), SGPT (ALT), SGOT (AST), total bilirubin, amylase, potassium, sodium, creatinine, glucose (hypo only), phosphate, albumin, calcium, magnesium, creatinine, direct bilirubin, blood urea nitrogen (BUN) or urea, GGT, lipase.
- For bi-directional parameters, both hyper and hypo summaries will be presented.

The following laboratory parameters will be presented in listings and will not be summarized:

- Urinalysis: macroscopic panel (dipstick) (bilirubin, blood, glucose, WBC, pH, protein, specific gravity), Urinalysis Microscopic panel (RBC, WBC, casts).
- Coagulation: INR, pro-thrombin time (PT) or Quick Test

The following listings will be produced for the laboratory data for all laboratory parameters where CTC grades are defined:

- Listing of participants with laboratory abnormalities of CTC grade 3,4, or 5
- Listing of all laboratory data with values flagged to show the corresponding CTC grades and the classifications relative to the laboratory reference ranges.

Liver function parameters

Liver function parameters of interest are total bilirubin (BILI), ALT, AST and alkaline phosphatase (ALP). The number and percentage of participants with worst post-baseline values as per Novartis Liver Toxicity guideline will be summarized by cohort. Because the study protocol inclusion criteria allowed participants to be enrolled with elevated baseline ALT or AST values, these are distinguished in the assessment.

The following summaries will be produced:

- Peak post-baseline values
  - ALT >3×ULN
  - ALT >5×ULN
  - ALT >10×ULN
  - ALT >20×ULN
  - AST >3×ULN
  - AST >5×ULN
  - AST >10×ULN
  - AST >20×ULN
  - ALT or AST >3×ULN
  - ALT or AST >5×ULN

- ALT or AST >8×ULN
- ALT or AST >10×ULN
- ALT or AST >20×ULN
- BILI >2×ULN
- BILI >3×ULN

– Combined elevations post-baseline
  - AST and ALT ≤ ULN at baseline
    - (ALT or AST >3×ULN) and BILI >2×ULN
    - (ALT or AST >3×ULN) and BILI >2×ULN and ALP ≥ 2×ULN
    - (ALT or AST >3× ULN) and BILI >2× ULN and ALP <2×ULN
  - ALT or AST >ULN at baseline
    - (Elevated ALT or AST) and BILI >2×BL and BILI >2×ULN
    - (Elevated ALT or AST) and BILI >2×BL and BILI >2×ULN and ALP ≥ 2×ULN
    - (Elevated ALT or AST) and BILI >2×BL and BILI >2×ULN and ALP <2×ULN

Combined elevations post-baseline are based on the peak values at any post-baseline time for a participant.

(Elevated AST or ALT) is defined as:
- >3×ULN if ≤ ULN at baseline, or
- (>3×BL or >8×ULN) if >ULN at baseline

Potential Hy's Law events are defined as those participants who, depending on their baseline status, fulfill one of the criteria. Further medical review has to be conducted to assess potential confounding factors such as liver metastases, liver function at baseline etc.

In addition, a listing by cohort of the hepatic laboratory values (TBL, ALT, AST and ALP) will be provided with values x.x times above ULN and CTCAE grades flagged. Peak total bilirubin vs peak ALT values will also be graphically presented (eDISH plot).

2.8.4 Other safety data

2.8.4.1 ECG and cardiac imaging data

ECG data will be analyzed based on central laboratory reported results by cohort. The summaries will include all ECG assessments performed no later than 30 days after the last date of study drug. All ECG assessments will be listed, and those collected later than 30 days after study drug discontinuation will be flagged in the listing.

Number and percentage of participants with notable ECG values will be presented by cohort. ECG shift table based on notable values will also be presented by cohort. The followings are the notable ECG values.

QT and 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 ≤ 60ms
- 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 value of > 120 ms

In addition, the following analysis will be carried out;

- Descriptive statistical analysis (mean and two-sided 90% confidence interval) by time point of assessment for ΔQTcF (QTcF change from baseline)
- A graphical presentation of ECG mean change from baseline over time will be produced based on time windows.

2.8.4.2 Vital signs

Vital sign assessments are performed in order to characterize basic body function. The following parameters were collected: height (cm), weight (kg), body temperature (°C), pulse rate (beats per minute), systolic and diastolic blood pressure (mmHg) (supine position preferred when ECG is collected).

Data handling

Vital signs collected on treatment will be summarized. Values measured outside of on treatment period will be flagged in the listings.

Data analysis

For analysis of vital signs, the clinically notable vital sign criteria are provided in Table 2-4 below.

Table 2-4 Clinically notable changes in vital signs

Vital sign (unit)	Clinically notable criteria	
	above normal value	**below normal value**
Weight (kg)	increase > 10% from Baseline	decrease > 10% from Baseline
Systolic blood pressure (mmHg)	≥180 and an increase ≥20 from baseline	≤90 and a decrease ≥20 from baseline

Vital sign (unit)	Clinically notable criteria	
	above normal value	**below normal value**
Diastolic blood pressure (mmHg)	≥105 and an increase ≥15 from baseline	≤50 and a decrease ≥15 from baseline
Pulse rate (bpm)	≥100 with increase from baseline of ≥25%	≤ 50 with decrease from baseline of ≥25%
Body temperature (°C)	≥39.1	≤ 35°C

Vital signs shift table based on values classified as notable low, normal, notable high or notable (high and low) at baseline and worst post-baseline will be produced for pulse rate, diastolic BP and systolic BP.

Baseline values (Low/high) are defined as:

- Systolic BP: ≤ 90 mmHg / Systolic BP: ≥ 180 mmHg
- Diastolic BP: ≤ 50 mmHg / Diastolic BP: ≥ 105 mmHg
- Body temperature: ≤ 35°C / Body temperature: ≥ 39.1°C
- Pulse rate: ≤ 50 bpm / Pulse rate: ≥ 100 bpm

The number and percentage of subjects with notable vital sign values (high/low) will be presented by cohort.

The following two listings will be produced by cohort:

- Participants with clinically notable vital sign abnormalities by cohort.
- All vital sign assessments will be listed by participant and vital sign parameter.

In both listings, the clinically notable values will be flagged and also the assessments collected later than 30 days after the last treatment/exposure date will be flagged.

2.8.4.3 ECOG performance status

The ECOG performance status assessment allows participants to be classified as to their functional impairment, the definition of scores in relation to their performance status is provided in Table 2-5, ranging from 0 (most active) to 5 (dead):

Table 2-5 ECOG Performance Scale

Score	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours

Score	Description
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Shift tables of ECOG performance status at baseline to worst or best post-baseline ECOG performance status by score will be provided by cohort using the safety set.

2.9 Pharmacokinetic

The PAS will be used in all tables and figures reporting pharmacokinetic data analysis and PK summary statistics by cohort.

2.9.1 Descriptive statistics for pharmacokinetics endpoints

Descriptive summary statistics of plasma concentration will be provided by cohort and by visit/sampling time point. Summary statistics will include mean (arithmetic and geometric), SD, CV% (arithmetic and geometric), median, minimum and maximum.

Capmatinib plasma concentration data will be listed by cohort, participant, and visit/sampling time point.

Concentration values below the lower limit of quantitation (LLOQ) will be displayed in listings as zero with a flag and handled as zero in any calculations of summary statistics, but handled as missing for the calculation of the geometric means and their CV.

If data permits, population PK analysis CCI .

2.10 PD and PK/PD analyses

Refer to Section 2.9

2.11 Patient-reported outcomes

Patient reported outcomes (PROs) including EORTC QLQ-C30/LC13 EQ-5D-5L and NCCN FACT-Brain Symptom Index (FBrSI) questionnaires will be summarized by cohort. The FAS will be used for analyzing PRO data. The baseline is defined as the last PRO assessment on or prior to randomization.

Descriptive statistics will be used to summarize the individual items and scored sub-scale scores at each scheduled assessment time point by cohort for EORTC QLQ-C30/LC13, EQ-5D-5L and NCCN FACT-Brain Symptom Index (FBrSI).

Scoring of PRO data and methods for handling of missing items or missing assessments will be handled according to the scoring manual and user guide for each respective patient questionnaire (Fayers 2001, Van Reenen 2015). No imputation procedures will be applied for

missing items or missing assessments. Changes from the baseline by cohort at each visit will be ploted for all scales of QLQ-LC13, QLQ-C30, EQ-5D-5L and FBrSI.

PRO Compliance and Completeness

Completion and compliance will be summarized for each scheduled assessment time point by cohort.

Windows for multiple assessments – PRO

Time windows (Table 2-6) are defined for descriptive summary of PRO data by visit and longitudinal data analysis. If more than one assessment is available in the same time window, the assessment closest to the planned date will be considered. If two assessments are obtained with the same time difference compared to the scheduled visit day, the assessment obtained prior to visit will be considered. Data obtained at the end of treatment (EOT) will be classified as other assessment in the corresponding time window. The EOT assessment will be included if collected within 30 days of the last dose intake.

Table 2-6 Time windows for PRO

Time Window	Planned Visit Timing	Time Window Definition
Cycle 1 Day 1/Baseline	Study Day 1	≤Study Days 1
Cycle 3 Day 1 (Week 7)	Study Day 43	Study Days 2 –63
Every 6 weeks thereafter	Scheduled visit day	Scheduled visit day ± 21 days

Study Day 1 = the first day of dosing

Additionally, change from baseline of EORTC QLQ-C30/LC13,EQ-5D-5L, and FBrSI-DRS-P in the domain scores at the time of each assessment will be summarized by cohort. Participants with an evaluable baseline score and at least one evaluable post baseline score during the treatment period will be included in the change from baseline analyses. These PRO scores will also be displayed as mean profiles of change from baseline for each cohort, presented over time using time windows.

Instead of using total score (FBrSI-24 total) which consists of 24 questions (range: 0-96), disease related symptom-physical score (FBrSI-DRS-P) will be used to define the secondary endpoint of change from baseline in symptoms of the brain metastases. FBrSI-DRS-P consists of 12 questions (range:0-48).

2.12 Biomarkers

As a project standard, only biomarker data collected in the clinical database will be analyzed. This study is not adequately powered to assess specific biomarker related hypotheses. The analyses of biomarkers will be reported in the CSR if data are available at the time of clinical database lock and CSR preparation. Otherwise, the results may be reported in a separate report document.

There may be circumstances when a decision is made to stop a sample collection, or not perform or discontinue the analysis of tumor samples due to either practical or strategic reasons (e.g.,

issues related to the quality and or quantity of samples. Under such circumstances, the number of samples may be inadequate to perform a rigorous data analysis and the available data will only be listed.

2.12.1 Outline of the data analysis

The proposed data analysis will be aligned with the secondary biomarker objective of the protocol:

- To evaluate the association between *METex14* mutation status as measured in ctDNA at baseline with ORR, DOR and PFS upon treatment with capmatinib

2.12.2 Data handling principles

Participants with EGFR wild type and ALK-negative rearrangement will be pre-screened for METex14 mutation status by a tumor tissue-based clinical trial assay (CTA) at the Novartis-designated centrallaboratory. Subjects with centrally determined METex14 mutant tumor statuswill be screened for clinical eligibility criteria as described in the original clinical trial protocol. Participants METex14 mutant status will also be tested by the ctDNA at baseline. There is a possibility that those participants whotested positive by CTA, may not be *METex14* positive by ctDNA. The following contingency table (Table 2.7) summaries the concordance and discordance between the tests. Any invalid results from *METex14* ctDNA testing will not be included in the contingency table. The table includes all test results from Cohort 1 and Cohort 2. A list of METex14 mutation result by ctDNA and tumor tissue sample will be summarized.

Table 2-7. Contingency table summarizing the ctDNA Test results and the CTA results at baseline.

		METex14 mutation positive by tumor tissue sample	
METex14 ctDNA results		*METex14* mutation positive	n_1
		METex14 mutation negative	n_2
		Total	N

1. n_1=number of participants with concordance between MET mutation positive by tumor sample and METex14 mutation positive by plasma sample (ctDNA)
2. n_2=number of participants with discordance between MET mutation positive by tumor sample and METex14 mutation negative by plasma sample (ctDNA)
3. N = total number of participants having both test results at baseline

2.12.3 Data analysis principles

2.12.3.1 Analysis set

The FAS will be used for all biomarker analyses. Unless otherwise specified, all statistical analyses of biomarker data will be performed on participants with biomarker data.

2.12.3.2 Basic tables, figures and listings

If the number of participants is considered large enough, the association between *METex14* mutation status and ctDNA will be estimated through concordance and discordance rate. The concordance rate and its exact binomial 95% CI (Clopper and Pearson 1934) will be provided. Concordance will be the proportion (n_1/N) of participant's *METex14* mutant status where tests by ctDNA and tumor tissue simple will have the same results, otherwise discordance.

The evaluation of ORR will be conducted based on BIRC and investigator assessment. ORR will be estimated and the exact binomial 95% CI (Clopper and Pearson 1934) will be provided by *METex14* ctDNA status.

DOR and PFS will be described in tabular and graphical format using Kaplan-Meier methods by ctDNA status (Table 2.7). In the Kaplan-Meier plot the number of participants at risk at certain time points will be shown on the plot. The estimated median (in months) along with 95% CIs, as well as 25th and 75th percentiles will be reported (Brookmeyer and Crowley 1982). In addition, Kaplan-Meier estimated probabilities with corresponding 95% CIs at several time points (including at least 3, 6, 12, and 18 months) will be summarized. These analyses will be performed separately based on BIRC assessment and based on investigator assessment.

2.13 Other Exploratory analyses

CCI [redacted]

2.14 Interim analysis

No interim analysis is planned for this study.

3 Sample size calculation

3.1 Primary endpoint(s)

Approximate 35 participants will be treated in this two-cohort study (cohort 1 ~ 15 participants and cohort 2~20 participants). With 15 participants in Cohort 1, the lower bound of exact binomial 95% CI for observed ORR will be at least 38.4% when observed ORR is 66.7%. Similarly, with 20 participants in Cohort 2, the lower bound of exact binomial 95% CI for ORR will be ≥ 19.1% when observed ORR is 40%.

Table 3-1 below shows the results from study [CINC280A2201] which will be used as a reference for sample size calculation.

Table 3-1 Objective response rate (ORR) and 95% lower confidence interval (LCI) (%) in study CINC280A2201

Line	n/N	Point estimate (%)	95% LCI (%)
1L	19/28	67.9	47.6
2/3L	28/69	40.6	28.9

In study [CINC280A2201], 67.9% ORR and 47.6% of its lower limit of 95% CI were observed from 28 participants in the treatment naive cohort. If 10 responders out of 15 participants are observed in this study, cohort 1, it will result ORR of 66.7%. The probability of observing ORR greater than 47.6% is at least 0.89. With 15 participants, Table 3-2 below shows the probability of observing ORR greater than 47.6%.

Table 3-2 Operating characteristics for cohort 1

Sample size	True ORR (%) in Chinese participants	Probability (%) that observed ORR > 47.6% (lower limit in A2201)
15	50	50.0
	55	65.4
	60	78.7
	65	88.7
	70	95.0
	75	98.3

Similarly, in study [CINC280A2201], 40.6% ORR and 28.9% of its lower limit of 95% CI were observed from 69 participants from the pre-treated cohort. If 8 responders out of 20 participants are observed in this study, cohort 2, it will result 40% ORR. The probability of observing ORR greater than 28.9% is at least 0.87. With 20 participants, Table 3-3 below shows the probability of observing ORR greater than 28.9%.

Table 3-3 Operating characteristics for cohort 2

Sample size	True ORR (%) in Chinese participants	Probability (%) that observed ORR > 28.9% (lower limit in A2201)
20	25	38.3
	30	58.4
	35	75.5
	40	87.4
	45	94.5
	50	99.4

4 Change to protocol specified analyses

No change from protocol specified analysis was made.

5 Appendix

5.1 Imputation rules

5.1.1 Study drug

The study drug is INC280/Capmatinib.

5.1.2 AE date imputation

The following missing dates will not be imputed

- Missing AE start dates
- AE start dates missing the year
- Partial/missing AE end dates

AE with uncertain relationship will be considered as treatment-emergent AE.

For other types of missing dates, the rules specified in Tables 5-1 to Table 5-2 will be used.

Table 5-1 AE/treatment date abbreviations

	Day	Month	Year
Partial Adverse Event Start Date	<not used>	AEM	AEY
Treatment Start Date (TRTSTD)	<not used>	TRTM	TRTY

Table 5-2 describes the possible combinations and their associated imputations. The upper text indicates the imputation (NC, A, B, C etc.) and the lower text the relationship of the AE start date to the treatment start date (TRTSTD).

Table 5-2 Imputation algorithm

	AEM MISSING	AEM < TRTM	AEM = TRTM	AEM > TRTM
AEY MISSING	NC Uncertain	NC Uncertain	NC Uncertain	NC Uncertain
AEY < TRTY	(D) Before TRTSTD	(C) Before TRTSTD	(C) Before TRTSTD	(C) Before TRTSTD
AEY = TRTY	(B) Uncertain	(C) Before TRTSTD	(B) Uncertain	(A) After TRTSTD
AEY > TRTY	(E) After TRTSTD	(A) After TRTSTD	(A) After TRTSTD	(A) After TRTSTD

The legend to the above table is shown in Table 5-3.

Table 5-3 Imputation algorithm legend

Relationship	
Before TRTSTD	Indicates AE start date prior to Treatment Start Date
After TRTSTD	Indicates AE start date after Treatment Start Date
Uncertain	Insufficient to determine the relationship of AE start date to Treatment Start Date
Imputation calculation	
NC / Blank	No convention/imputation

Relationship	
(A)	01MONYYYY
(B)	TRTSTD+1
(C)	15MONYYYY
(D)	01JULYYYY
(E)	01JANYYYY

A few examples are shown in Table 5-4.

Table 5-4 Example scenarios

Partial AE start date	Treatment start date	Relationship with TRTSTD	Imputation Calculation	Imputed Date
12MMMYYYY	20OCT2001	Uncertain	NC	<blank>
DDMMM2000	20OCT2001	Before	(D)	01JUL2000
DDMMM2002	20OCT2001	After	(E)	01JAN2002
DDMMM2001	20OCT2001	Uncertain	(B)	21OCT2001
DDSEP2001	20OCT2001	Before	(C)	15SEP2001
DDOCT2001	20OCT2001	Uncertain	(B)	21OCT2001
DDNOV2001	20OCT2001	After	(A)	01NOV2001

5.1.3 Concomitant medication date imputation

The imputation of the start date of concomitant medication will follow the same conventions as for AE dates. Partial concomitant medication end dates will not be imputed.

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 for scenario (B) it will be replaced with "start date of study drug −1".

End date

- Imputed date = min (reference end date, last day of the month), if day is missing
- Imputed date = min (reference end date, 31DEC), if month and day are missing

Reference end date will be the start date of study drug.

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.

Incomplete date of progression –Prior antineoplastic therapy-medication

A missing day is defaulted to the 1st of the month. However, date of progression should be expected to be after start date of prior antineoplastic therapy.

- Imputed date = max (start date of prior antineoplastic therapy, 1st day of the month), if day is missing

5.1.3.2 Post therapies date imputation

Start date

- Imputed date = max (reference start date, first day of the month), if day is missing
- Imputed date = max (reference start date, 01JAN), if day and month are missing

Reference start date will be the last date of study treatment administration + 1.

End date

No imputation.

5.1.3.3 Other imputations

Incomplete date of initial diagnosis of cancer and date of most recent recurrence

A missing day is defaulted to the 15th of the month and a missing month and day is defaulted to 01JAN.

If because of this imputation the chronology of the events is altered then the imputation should be made to the minimum value up to where chronology remains unchanged. E.g. if due to imputation the date of most recent recurrence becomes prior to the initial diagnosis date then it should be set to initial diagnosis date.

Incomplete assessment dates for tumor assessment

All investigation dates (e.g. MRI scan, CT scan) must be completed with day, month and year. If one or more assessment dates are incomplete but other investigation dates are available, the incomplete date(s) are not considered for calculation of the assessment date and assessment date is calculated as the latest of all investigation dates (e.g. MRI scan, CT-scan) if the overall lesion response at that assessment is CR/PR/SD/UNK. Otherwise – if overall response is progression – the assessment date is calculated as the earliest date of all investigation dates at that evaluation number. If all measurement dates have no day recorded, the 1st of the month is used. If the month is not completed, for any of the investigations, the respective assessment will be considered to be at the date which is exactly between the previous and the following assessment. If a previous and following assessment is not available, this assessment will not be used for any calculation.

Incomplete or missing death date

For cases when either day is missing or both month and day are missing for the date of death, the following imputation rules will be implemented:

- If only day is missing, then impute 15th day of the month and year of death.
- If both day and month are missing, then impute 01JUL of the year of death.

5.2 Dose interruptions and changes

This section provides additional details to those included in Section 2.5.2.

All calculations of dose interruptions and dose changes are based on the dose actually taken by the participant.

An interruption is defined as a 0 mg dose taken on one or more days between two non-zero dosing periods. The last zero dose of INC280 followed by permanent discontinuation are not considered as dose interruption.

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

- If an interruption occurs consecutively for at least two days due to the same reason, then it will be counted only once (*example: If the actual dose on days 1-3 is 800 mg and actual dose on days 4-5 is 0 mg and dose interruption on days 4-5 is due to AE, then the total number of dose interruptions is 1*).
- If an interruption occurs consecutively for at least two days due to different reasons, then it will be counted for each reason (*example: If the actual dose on days 1-3 is 800 mg and actual dose on days 4-5 is 0 mg and dose interruption on day 4 is due to AE and dose interruption on day 5 is due to dosing error, then the total number of dose interruptions is 2*).
- If an interruption occurs for more than one day due to the same reason, but the days are not consecutive, i.e. there is at least one dosing day in between, then each dose interruption will be counted as a different occurrence (*example: if the actual dose on days 1, 3 and 5, is 800 mg and actual dose on days 2 and 4 is 0mg, and dose interruptions on day 2 and 4 are both due to dosing error, the total number of dose interruptions is 2*).

A dose change is defined as a change in dosing from one record to the next, however a dose interruption will not be counted as a dose change.

Dose reductions are a subset of dose changes where the total daily dose is lower than the previous non-zero dose.

Case 1: If a participant did not receive the protocol planned dose for any reason, then this is a dose reduction (400 mg, 800 mg).

Patient ID	Start date	End date	Dose	Regimen	Reason	Reduction (derived)	Comments
0001	22/03/2017	25/03/2017	400	ONCE PER DAY	DOSING ERROR	**Y**	1st administration different from protocol planned dose (800 mg)
	26/03/2017	26/05/2017	800	2 TIMES PER DAY			

Case 2: If, due to a dosing error, a participant receives higher than protocol planned dose and moves down to the planned dose then this is not a dose reduction (800 mg, 1000 mg, 800 mg); However if the change is directly from a higher than planned dose down to a lower than protocol planned dose, then this is a dose reduction (e.g. In the sequence, 800 mg, 1000 mg, 400 mg, is a dose ec$).

Patient ID	Start date	End date	Dose	Regimen	Reason	Reduction (derived)	Comments
0002	22/03/2017	21/05/2017	800	2 TIMES PER DAY			
	22/05/2017	23/05/2017	0		ADVERSE EVENT		
	24/05/2017	01/08/2017	600	2 TIMES PER DAY	ADVERSE EVENT	Y	
	02/08/2017	02/08/2017	700	2 TIMES PER DAY	DOSING ERROR		
	03/08/2017	05/08/2017	800	2 TIMES PER DAY			
	06/08/2017	06/08/2017	**1000**	**2 TIMES PER DAY**	**DOSING ERROR**		
	07/08/2017	12/09/2017	**800**	**2 TIMES PER DAY**		**N**	moves down to the dose administered just before dosing error
0003	22/03/2017	21/05/2017	800	2 TIMES PER DAY			
	22/05/2017	23/05/2017	0		ADVERSE EVENT		
	24/05/2017	01/08/2017	600	2 TIMES PER DAY	ADVERSE EVENT	Y	
	02/08/2017	02/08/2017	700	2 TIMES PER DAY	DOSING ERROR		
	03/08/2017	05/08/2017	800	2 TIMES PER DAY			
	06/08/2017	06/08/2017	**1000**	**2 TIMES PER DAY**	**DOSING ERROR**		
	07/08/2017	12/09/2017	**600**	**2 TIMES PER DAY**		**Y**	moves down to a lower dose administered just before dosing error

Case 3: If due to interruption, a participant receives half of the dose during 1 day and followed by an interruption (due to the same reason) then this is not a dose reduction (for ex: 800 mg 2 times per day from 27-Dec-2016 to 14-Jan-2018, and 400 mg once per day on 15-Jan-2018 and then interruption 16-Jan-2018 to 22-Jan-2018). After interruption, dose reduction will be determined using the dose received on a day without interruption (for ex: 600 mg vs 800 mg ignoring 400 mg on 15-Jan given it is related to the interruption).

Patient ID	Start date	End date	Dose	Regimen	Reason	Reduction (derived)	Comments
0004	27/12/2017	14/01/2018	800	2 TIMES PER DAY			
	15/01/2018	15/01/2018	**400**	**ONCE PER DAY**	**ADVERSE EVENT**	**N**	½ dose for 1 day same reason than interruption Interruption started on 15-Jan
	16/01/2018	22/01/2018	0		**ADVERSE EVENT**		
	23/01/2018	07/02/2018	600	2 TIMES PER DAY	ADVERSE EVENT	**Y**	Dose reduction from 800 mg to 600 mg [400 mg on 15Jan ignored for reduction determination as part of the interruption]
	08/02/2018	19/02/2018	0		ADVERSE EVENT		

Patient ID	Start date	End date	Dose	Regimen	Reason	Reduction (derived)	Comments
0005	25/04/2016	22/05/2016	800	2 TIMES PER DAY			
	23/05/2016	23/05/2016	400	ONCE PER DAY	ADVERSE EVENT	N	½ dose for 1 day same reason than interruption Interruption started on 23-May
	24/05/2016	25/05/2016	0		ADVERSE EVENT		
	26/05/2016	26/05/2016	400	ONCE PER DAY	ADVERSE EVENT	Y	Dose reduction from 800 mg to 400 mg [400 mg on 23May ignored for reduction determination as part of the interruption]
	27/05/2016	05/06/2016	800	2 TIMES PER DAY			
	06/06/2016	06/06/2016	400	ONCE PER DAY	DOSING ERROR	Y	
	07/06/2016	01/08/2016	800	2 TIMES PER DAY			
	02/08/2016	02/08/2016	400	**ONCE PER DAY**	**DOSING ERROR**	**Y**	½ dose for 1 day different reason than interruption
	03/08/2016	07/08/2016	0		**ADVERSE EVENT**		

Case 4: If due to permanent discontinuation, a pa receives half of the dose the last day of treatment then this is not a dose reduction (for ex: 800 mg 2 times per day from 30-May-2016 to 03-Oct-2016, and 400 mg once per day on 04-Oct-2016). This rule is applied for any dose levels (for ex: 600 mg 2 times per day from 15-Dec-2017 to 20-Dec-2017, and 300 mg once per day on 04-Oct-2016).

Patient ID	Start date	End date	Dose	Regimen	Reason	Permanently discontinuation	Reduction (derived)
0006	30/05/2016	03/10/2016	800	2 TIMES PER DAY			
	04/10/2016	04/10/2016	400	ONCE PER DAY	ADVERSE EVENT	Y	N

5.3 Implementation of RECIST guidelines

Disease progression

PD should only be assigned if it is confirmed by an objective assessment method as per RECIST 1.1 (e.g. radiologic scan, histology for bronchoscopy, photos for skin lesions). If a new lesion is detected using an objective assessment method other than radiologic scan, it should be entered on the 'New lesion' RECIST eCRF with appropriate method (or method= 'Other').

In particular, discontinuation due to disease progression or death due to progressive disease, without supporting objective evidence (as defined above), will not be considered as PD in the determination of BOR, the derivation of any efficacy endpoint or efficacy analysis.

Change in imaging modality

Per RECIST 1.1, a change in methodology can be defined as either a change in contrast use (e.g. keeping the same technique, like CT, but switching from with to without contrast use or vice-versa, regardless of the justification for the change) or a change in technique (e.g. from CT to MRI, or vice-versa), or a change in any other imaging modality. A change from conventional to spiral CT and vice versa while keeping same contrast use (e.g. switching from spiral CT with contrast to CT with contrast) is not considered a change in imaging modality. A change in methodology will result by default in a UNK (unknown) overall lesion response assessment. However, a response assessment other than the Novartis calculated UNK response may be accepted from the investigator or BIRC if a definitive response assessment can be justified based on the available information. Potential discrepancies between the modality used and overall lesion response reported by the investigator (e.g. change in modality but investigator assessment of response is different from UNK) will be queried during the data validation process.

Determination of missing adequate tumor assessments

For the computation of ORR, participants without any radiological assessment after the start date of study drug will be counted as failure.

Partial or complete responses reported prior to any additional anticancer therapy will be considered for ORR computation irrespective of the number of missed assessments before response. In this section, the 'missing adequate assessment' is defined as assessment not done or assessment with overall lesion response equal to UNK. For the sake of simplicity, the 'missing adequate assessment' will also be referred as 'missing assessment'.

The PFS censoring and event date options depend on the presence and the number of missing tumor assessments. For example, an event occurring after two or more missing assessments is censored in the analysis of PFS at the last adequate tumor assessment before the event date.

An exact rule to determine whether there is none, one or two missing assessments is therefore needed. This rule will be based on the distance between the last adequate tumor assessment date and the event date.

If the distance is larger than threshold D_1 or D_2 then the analysis will assume one or two missing assessments, respectively. The threshold D_1 will be defined as the protocol specified interval between the tumor assessments plus the protocol allowed window around the assessments. Similarly, the threshold D_2 is defined as two times the protocol specified interval between the tumor assessments plus the protocol allowed window around the assessments. In this study, the protocol defined schedule of tumor assessment is every 6 weeks and each assessment is expected to be performed at the scheduled time point plus or minus 1 week, i.e. the window is 2 weeks, then any distance larger than $D_1 = 6+2 = 8$ weeks means one missing assessment and any distance larger than $D_2 = (2*6) + 2 = 14$ weeks means two missing assessments.

The same definition of D_2 will be used to determine the PFS censoring reason.

Possible censoring reasons for PFS are:

1: Ongoing without event

2: Lost to follow-up
3: Withdrew consent
4: Adequate assessment no longer available
5: New cancer therapy added
6: Event after >=2 missing tumor assessments

PFS censoring reason is then derived by the following sequence of rules.

- If participant is considered to have a PFS event then PFS censoring reason is set to missing.
- Else if participant has had no baseline assessment then PFS censoring reason = 4.
- Else if participant has a PFS event after two or more missing assessments [If (PFS Event date ≤ Censoring date and (PFS Event date - Date of last adequate tumor assessment (LATA) ≥ D2)] then PFS censoring reason =6:
- Else if participant has no PFS event, and participant is censored at a date after two or more missing assessments ((Censoring date - Date of LATA) ≥ D2) then PFS censoring reason = 4
- Else if censoring date equals the start date of further anti-neoplastic therapy then PFS censoring reason = 5
- Else if censoring date equals date of discontinuation due to consent withdrawal then PFS censoring reason = 3
- Else if censoring date equals date of discontinuation due to loss to follow-up then PFS censoring reason = 2
- Else if the censoring date equal the analysis cut-off date and the time between LATA and the cut-off is greater than D2 days then PFS censoring reason = 4
- Else if the censoring date equal the analysis cut-off date and the time between LATA and the cut-off is less than or equal to D2 days then PFS censoring reason = 1

Where censoring date = minimum (analysis cut-off date, start date of further anti-neoplastic therapy, date of discontinuation due to consent withdrawal, date of discontinuation due to loss to follow-up).

Non-measurable disease at baseline

If a participant without measurable disease is enrolled, the intent-to-treat (ITT) principle requires including these participants in the analyses. Hence, analyses will be based on FAS including participants with either measurable or non-measurable disease. Therefore, a rule needs to be specified on how to handle these cases.

Overall lesion response can be derived for participants without measurable disease at baseline as follows (Table 5-5).

Table 5-5 Overall lesion response at each assessment: participants with non-target disease only

Non-target lesions	New Lesions	Overall lesion response
CR	No	CR
Non-CR/Non-PD[1]	No	Non-CR/non-PD
UNK	No	UNK
PD	Yes or No	PD
Any	Yes	PD

[1] In general, the **non-CR/non-PD response** for these participants is considered equivalent to an SD response in endpoint determination.

Missing baseline tumor assessment

As specified in Section 14 (Appendix II) of the protocol, since the timing of PD cannot be determined for participants with missing baseline tumor assessment, these participants are censored in the PFS analysis at the start date of treatment. This rule, however, only applies to the 'PD component' of the PFS or DOR assessment.

Participants without baseline tumor assessment who die within D_2 distance from start date of treatment will be counted as having an event in the analysis of PFS. All deaths will be counted in the OS analysis regardless of presence or absence of the baseline tumor assessment.

5.4 Patient reported outcomes: EORTC QLQ-C30/LC13, EQ-5D-5L and NCCN FACT-Brain Symptom Index (FBrSI)

The text below gives more detailed instructions and rules needed for programming of the analyses described in Section 2.11.

EORTC QLQ-C30 scale scores will be generated by first obtaining the raw scores adding up the item responses on the questions which make up each domain and then applying the linear transformation to the raw scores in accordance with the respective scoring manual provided by the developers (Fayers 2001). Scores in each scale will be generated if at least half of the items comprising the scale have been answered. For single item scales with missing responses and scales where less than half of the items have not been answered, scale scores will be set to missing.

The scoring approach for the QLQ-LC13 is identical in principle to that for the symptom scales/single items of the QLQ-C30. The dyspnea scale of the QLQ-LC13 is the only multi item scale (all others are single item scales) and should only be used if all items comprising the scale have been answered.

The number of participants filling the PRO questionnaires and the number of participants missing PRO assessments out of those eligible to have PRO assessments will be summarized for scheduled assessment time points. The following categories will be used to describe whether the questionnaire was completed at a specific time point:

- yes, fully completed

- yes, partially completed
- no, participant missed scheduled assessment visit
- no, participant refused due to poor health
- no, participant refused (unrelated to health)
- no, study staff felt participant was too ill
- no, questionnaire not available in appropriate language
- no, institutional error
- no, other

EQ-5D-5L (Van Reenen M et al., 2019) consists of 5 questions (5D) with possible choices to answer of any question is 5 (5L). Each participant will be asked about mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The lower the score is the better the outcome for the participant.

NCCN Brain Symptom Index-24 (FBrSI-24) [Lai JS et al., 2014] consists of twenty-four questions. All questions are in 5-point likert scale (0-4) of which some of them are in positive direction and some of them are negative direction. All scores will be converted to positive direction for the statistical analysis and interpretation of the results, following the NFBrSI-SRS-P guidelines in section 7.1.1. Higher score indicates better outcome.
After converting each item score in positive direction, the following formula will be used to get the final score for each participant:

$$FBrSI - 24\ score = \frac{sum\ of\ individual\ item\ scores \times 24}{Number\ of\ item\ answered}$$

FBrSI-DRS-P (Disease Related Symptom-Physical) consists of 12 questions (range:0-48). All questions are in 5-point likert scale (0-4). All scores will be converted to positive direction for statistical analysis and interpretation. Higher score indicates better outcome. Only on-treatment period will be considered.

After converting each item score in positive direction, the following formula will be used to get the final score for each participant:

$$FBrSI - DRS - P = \frac{sum\ of\ individual\ item\ scores \times 12}{Number\ of\ item\ answered}$$

5.5 Adverse events data

5.5.1 Coding of AEs

Adverse events are coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

5.5.2 Grading of AEs

AEs will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.

The CTCAE represents a comprehensive grading system for reporting the acute and late effects of cancer treatments. CTCAE version 5 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).

If CTCAE grading does not exist for an adverse event, grades 1 – 5 corresponding to the severity of mild, moderate, severe, life-threatening, and death will be used.

5.6 Laboratory parameters derivations

This section provides further detail on the analysis of laboratory parameters that will be listed and summarized as described in Section 2.8.3.

5.6.1 Hematology

Hematologic tests include: Hemoglobin, platelets, white blood cells (WBC), red blood cells (RBC), differential (basophils, eosinophils, lymphocytes, and monocytes, neutrophils (% or absolute)

The following rules will be applied to derive the WBC differential counts when only percentages are available (this is mainly for neutrophils and lymphocytes, because CTC grading is based on the absolute counts).

The method to convert the value is straightforward: for each participant, the original lab value (%) is divided by 100 and multiplied by WBC count e.g. for neutrophils (NEU):

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

In order to derive the corresponding absolute normal range, the rule to be applied depends on the availability of the % range and the absolute range for the differential:

- If % absolute range NOT missing (% range is or isn't missing), then use the absolute range provided by the site
- If % range NOT missing and absolute range missing, then the % normal limits (i.e. LLN and ULN) are divided by 100 and multiplied by the corresponding normal limits of WBC count, e.g. for neutrophils NEU):

  LLN for NEU count = (LLN for WBC count) * (LLN for NEU%value /100)

  ULN for NEU count = (ULN for WBC count) *(ULN for NEU%value/100)

5.6.2 Biochemistry

The following calculation will be applied for corrected calcium in SI unit (if not available in the Lab database):

Corrected calcium (mmol/L) =measured total Ca (mmol/L) +0.02 (40-serum albumin[g/L]), where 40 represents the average albumin level in g/L.

Time windows will be defined for trends of labs over time.

Table 5-6 Time windows for Labs

Time Window	Planned Visit Timing	Time Window Definition
Baseline	On or before Study Day 1	≤ Study Day 1
Cycle 1 Day 15 (Week 3)	Study Day 15	Study Days 2 – 18
Cycle 2 Day 1 (Week 4)	Study Day 22	Study Days 19 – 32
Cycle 3 Day 1 (Week 7)	Study Day 43	Study Days 33 – 53
Cycle 4 Day 1 (Week 10)	Study Day 64	Study Days 54 – 74
Cycle 5 Day 1 (Week 13)	Study Day 85	Study Days 75 – 95
Cycle 6 Day 1 (Week 16)	Study Day 106	Study Days 96 – 116
Cycle 7 Day 1 (Week 19)	Study Day 127	Study Days 117 – 137
Each and every cycle thereafter until EOT	Scheduled visit day (+ 21 days from previous cycle)	Scheduled visit day ± 10 days centered around the planned assessment

Study Day 1 = the first day of dosing

5.7 Statistical models

5.7.1 Primary analysis

The estimate of the response rates (e.g., ORR,) will be summarized in terms of percentage rates with 95% CIs. An exact binomial confidence interval (implemented using SAS procedure FREQ with EXACT statement for one-way tables) will be calculated (Clopper and Pearson 1934).

SAS procedure FREQ will be used to estimate the proportion of responders (binary outcome = 1 or "Yes"), along with the associated 95% (=100 × (1 – *two-sided alpha level*)) two-sided exact binomial CI. These estimates are obtained as follows:

```
proc freq data = dataset;
      table binary event /
            binomial(
                  level = "Yes")
            alpha = two-sided alpha level;
      exact binomial;
```

When there are no responders, SAS does not produce a CI by default. To obtain a CI in this situation, PROC FREQ is used as specified above except changing **level**="No". From the results of this modified procedure, the values in percent of the LCL and UCL of a 0% response rate are calculated as follows:

$$LCL_{LEVEL="Yes"}\ (\%) = 100\% - UCL_{LEVEL="No"}\ (\%)$$

$$UCL_{LEVEL="Yes"}\ (\%) = 100\% - LCL_{LEVEL="No"}\ (\%)$$

6 Reference

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7 Appendix

7.1.1 NCCN/FACT-BrSI Scoring Guidelines

FBrSI-DRS-P Scoring Guidelines

Instructions:* 1. Record answers in "item response" column. If missing, mark with an X

2. Perform reversals as indicated, and sum individual items to obtain a score.

3. Multiply the sum of the item scores by the number of items in the subscale, then divide by the number of items answered. This produces the subscale score.

4. The higher the score, the better the QOL.

Subscale	Item Code	Reverse item?		Item response	Item Score
Disease related Symptom - physical (FBrSI-DRS-P)	An10	4	-	_____	=_____
	Ar21	4	-	_____	=_____
	Br2	4	-	_____	=_____
	Br14	4	-	_____	=_____
Score range: 0-48	Br20	4	-	_____	=_____
	C2	4	-	_____	=_____
	GP3	4	-	_____	=_____
	Br9	4	-	_____	=_____
	GF5	0	+	_____	=_____
	Br1	0	+	_____	=_____
	Br3	0	+	_____	=_____
	Br8	0	+	_____	=_____

Sum individual item scores: _____

Multiply by 12: _____

Divide by number of items answered: _____ =***FBrSI-DRS-P subscale score***