NOVARTIS

Clinical Development

INC280/Capmatinib

CINC280AIN01 / NCT05110196

A Prospective, Multicenter, Open-label, Phase IV, Interventional Study to Assess the Safety and Efficacy of Capmatinib in Indian Patients with Mesenchymal- Epithelial Transition (MET) exon 14 Skipping Mutation Positive Metastatic Non-Small Cell Lung Cancer (NSCLC)

Statistical Analysis Plan (SAP)

Author: [redacted]
Document type: SAP Documentation
Document status: Version 01
Clinical trial phase: IV
Release date: 07 Nov 2025
Number of pages: 38

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Template Version 6.0, Effective from 23-Nov-2022

[redacted]

DocUUID : 7db2c701-4fe9-41f0-8e64-0e9050784bb2

SAP Template History

- Version 1.0- Final version 24-Sep-2015, Effective 31-Oct-2015
    - Initial SAP template
- *Version 2.0- Final version 25-Apr-2016, Effective 03-May-2016*
    - *SAP template updated with instructions included on SAP review and approval process*
- *Version 3.0 – Final version 10-Jun-2020, Effective 01-July-2020*
    - *Author removed from SAP cover page*
    - *CREDI changed to DMS*
    - *Use "subject" or "participant" (not "Subject") to align with OneCTP*
    - *SAP posted to Registries so no personal information on trial participant should be included.*
    - *SAP can be included as is in CSR Appendix 16.1.9*
    - *Reference to SMART SAP LEANing principles*
    - *TP and MW added as Approvers for SAP*
    - *Post DBL data-drive analyses must be included in a SAP and/or TFL Shells Addendum if the analyses are to be included in the CSR*
    - *"Investigational" treatment term used instead of study/trial treatment*
    - *Only subgroup analyses addressing the key study objectives (and included in the CSR) should to be described in the SAP*
    - *Do separate analyses for pediatrics and adults if both populations are included in the study*
    - *Guidance on language that allows the flexibility to conduct primary analysis when a target sample size based on overall study population has been attained*
    - *State which population is considered primary based on the primary endpoint estimand definition.*
    - *Exploratory objectives do not need to be addressed in the CSR*
- *Version 4.0 – Final version 23-Apr-2021, Effective 23-Apr-2021*
    - *In introduction section 1, added sections for definition of primary estimands and secondary estimands. Ensure study design description is in alignment with the chosen estimands.*
    - *Analysis sets definition should be aligned with the population attributes of the chosen estimands. Per-protocol set should be used with caution under estimand framework, as E9(R1) highlights the difficulties with a naïve analysis of the per-protocol set. In section 5.5, Table 1 'Protocol deviations that cause subjects to*

be excluded' was removed; in Table 2, column of 'PD ID that cause subjects to be excluded' and row of PPS were removed.

- *Supportive analysis is split into sensitivity analysis and supplementary analysis. Subgroup analysis in section 2.2.1 belongs to supplementary analysis.*
- *Created a subsection for analysis of demographics and other baseline characteristics.*
- *Treatment attribute of the estimands (treatment of interest) may be different from investigational treatment. Analysis of treatment of interest may be necessary to interpret efficacy/safety analyses.*
- *Structures for section 2.5 and 2.6 were updated according to OneCTP to align with estimand framework.*
- *Used 'analysis supporting primary/secondary objectives' (not 'analysis of the primary objective')*
- *Removed section of analysis of the key secondary objective to align with OneCTP*

- *Version 5.0 – Final version 23-Sep-2022, Effective 23-sep-2022*

  Template was updated due to the Template classification project:

  - *existing classification was updated based on the information from the Template Owner – for example: from Confidential to Business Use Only).*
  - *(if needed) Novartis logo and Novstyle version were updated*

- *Version 6.0 – Effective 23-Nov-2022*

  Template confidentiality classification was corrected from Restricted to Confidential.

Document History – Changes compared to previous final version of SAP

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
07 Nov 2025	Initial Version	NA	N/A - First version	NA

Signatures:

[redacted] Dr. [redacted]
10 Nov 2025 09:21:34 (+05:30)
REASON: I am approving this document.
2b9da0bd-9dc2-47da-8fb5-ff7a8aa05a66

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Date: 07 November 2025

[redacted] Dr. [redacted]
07 Nov 2025 11:38:05 (+05:30)
REASON: I am approving this document.
de2d1137-ced6-4850-bbca-1e42cf84f3c2

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Date: 07 November 2025

[redacted] [redacted] 10 Nov 2025 20:43:47 (+05:30)
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60e52f94-1e9b-4add-9a3f-32174b2b0087

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Date: 07 November 2025

[redacted] [redacted] 10 Nov 2025 16:29:35 (+05:30)
REASON: I am approving this document.
26c586d8-00be-4501-9b27-834029090a1c

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[redacted] [redacted] 11 Nov 2025 10:24:51 (+05:30)
REASON: I am approving this document.
e7636d49-83d6-45b0-8cc3-df8e494abad8

Dr. [redacted]

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Date: 07 November 2025

[redacted] 09 Nov 2025 16:37:58 (+05:30)
REASON: I am approving this document.
8619229d-e6ae-4998-b2f9-bde29669f341
[redacted]
Date: 07 November 2025

[redacted] 07 Nov 2025 11:10:05 (+05:30)
REASON: I have prepared this document
d9a6f562-4732-44fd-a9a0-23267a202f7e
[redacted]
Date: 07 November 2025

[redacted] 07 Nov 2025 11:28:29 (+05:30)
REASON: I have reviewed this document.
bcf01afd-a1e7-4723-860f-6c3324284a38
[redacted]
Date: 07 November 2025

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List of abbreviations

AE	Adverse Event
ALK	Anaplastic lymphoma kinase
ALP	Alkaline Phosphatase
ALT	Alanine Transaminase
AST	Aspartate Transaminase
BID	Bis in die/twice a day
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
eCRF	Electronic Case Report/Record Form
ECG	Electrocardiogram
EGFR	Epidermal Growth Factor Receptor
EOS	End of Study
EOT	End of Treatment
FAS	Full Analysis Set
GGT	Gamma-Glutamyl Transferase
IA	Interim Analyses
ICF	Informed Consent Form
MedDRA	Medical Dictionary for Drug Regulatory Affairs
PK	Pharmacokinetics
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SD	Stable Disease
TFLs	Tables, Figures, Listings
TTR	Time to Response
WHO	World Health Organization
DCGI	Drugs Controller General of India
DCR	Disease control Rate
DOR	Duration of Response
ECG	Electrocardiogram
MET	Mesenchymal epithelial transition
NSCLC	Non-small cell lung cancer
OIRR	Overall intracranial response rate;
ORR	Overall response rate
PFS	Progression free survival
PR	Partial Response
PS	Performance Status
PTA	Post-trial access
QTcF	QT interval corrected by Fridericia's formula
RANO	Response Assessment in Neuro-Oncology
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
TEAE	Treatment Emergent Adverse Event

TTR	Time to response

1 Introduction

This document (Statistical Analysis Plan) provides the technical and detailed elaboration of the analytical details mentioned in the CINC280AIN01, Phase IV, prospective, multicenter, open-label, interventional study to assess the safety and efficacy of capmatinib in Indian patients with MET exon 14 skipping mutation positive metastatic NSCLC in any line of therapy.

The main objective of this plan is to provide detailed information of statistical methodology, data conventions, and processes used for the analysis of data from the study.The total study duration for 50 patients in the study will be approximately 2.5 years.

1.1 Study design

This is a Phase IV, prospective, multicenter, open-label, interventional study to assess the safety and efficacy of capmatinib in Indian patients with MET exon 14 skipping mutation positive metastatic NSCLC in any line of therapy. The study will include approximately 50 patients. During the treatment period, study treatment will be administered as capmatinib 400 mg orally as twice daily (BID) on a continuous dosing schedule for 24 weeks.

The study includes molecular pre-screening for detection of MET exon 14 skipping mutation and confirming Epidermal Growth Factor Receptor (EGFR)-wild type (EGFR Negative) and negative Anaplastic lymphoma kinase (ALK) rearrangement (will be done for patient who don't have local test reports. For patients who already have available local test reports they can be directly screened for the main study), screening (Day-28 to Day -1), treatment period of 24 weeks, end of treatment (EOT) visit evaluation after 24 weeks or early discontinuation of treatment (whichever is earlier), and follow-up period of 30 days post the last dose of the study treatment. Completion of the follow-up period after the last dose of the study treatment will be considered as the End of Study (EOS). Patients transitioning to post trial access (PTA) will also have to compete the EOS Visit assessment after the last dose administration of capmatinib (which is as a part 6 months of treatment) for the current study.

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Patients may be discontinued from treatment earlier due to unacceptable toxicity, disease progression, withdrawal of consent, or at the discretion of the investigator or the patient. These patients will have EOS assessment 30 days after the administration of last dose of the study treatment.

Every effort will be made by Novartis to continue provision of study treatment capmatinib via post trial access (PTA) to the patients who are ongoing on treatment at the end of the planned duration of study and deriving clinical benefit from capmatinib in the opinion of the investigator. Patients entering PTA will have a seamless transition without any interruption.

- **Study Design Rationale**

The DCGI has granted approval for Rahika® (Capmatinib) film-coated tablet 150 mg and 200 mg for the treatment of adult patients with metastatic NSCLC whose tumors have a mutation that leads to MET exon 14 skipping mutation with condition to perform a Phase IV clinical trial in Indian patients.

As recommended by DCGI, this Phase IV study has been planned to evaluate the safety and efficacy of capmatinib in treatment of adult Indian patients with metastatic NSCLC whose tumors have a MET exon 14 skipping mutation.

- **Study Treatments**

This Phase IV study will be an open-label and single-arm study. All the eligible patients will be assigned to the study treatment (capmatinib 400 mg BID orally) from C1D1. The treatment with capmatinib will be started only when the previous anti-cancer treatment was stopped within 4 weeks or ≥5 x half-life (whichever is longer) in subject who were on prior line/s of treatment. The treatment period begins on Day 1 of Cycle 1. Each treatment cycle will be of 21 days. The first dose of capmatinib will be administered at the study center. All patients will be treated with 400 mg capmatinib tablets BID, administered orally on a continuous dosing schedule. Cycle 2 will start on Day 22 of the study and will be considered as Cycle 2 Day 22 (C2D22) and so on if there is no temporary discontinuation. Planned treatment duration for this study is 6 months (24 weeks) of capmatinib therapy and patients will be followed up for assessment of clinical outcomes.

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1.2 Study objectives, endpoints

Objectives	End points
Primary Objective	**Endpoints for primary objective**
• To assess the safety of capmatinib in Indian patients with MET exon 14 skipping mutation positive metastatic NSCLC	• Incidence of AEs, including SAEs after treatment initiation, changes in laboratory values, vital signs, and ECGs • Tolerability: dose interruptions, reductions, and dose intensity
Secondary Objective	**Endpoints for secondary objective**
• To assess the efficacy of capmatinib in Indian patients with MET exon 14 skipping mutation positive metastatic NSCLC	• All assessed per RECIST 1.1 by investigator assessment# • ORR • OIRR • DOR • TTR • DCR • PFS

AE=Adverse event; DCR=disease control rate; DOR=Duration of response; ECG=Electrocardiogram; MET=Mesenchymal epithelial transition; NSCLC= Non-small cell lung cancer; OIRR=Overall intracranial response rate; ORR=Overall response rate; PFS=Progression free survival; RECIST=Response Evaluation Criteria in Solid Tumors; SAE=Serious adverse event; TTR=Time to response.

Tumor assessment by RECIST 1.1 performed every 6 weeks by investigator from the first day of treatment with capmatinib until disease progression.

1.2.1 Primary estimand(s)

NA

1.2.2 Secondary estimand(s)

NA

2 Statistical methods

2.1 Data analysis general information

Analysis of the data will be performed by the Biostatistics and Statistical Programming team at [redacted] All statistical analyses will be performed using SAS® Enterprise Guide® 7.1.

The following standard descriptive analyses will be presented for all analysis populations:

- Descriptive statistics for continuous data

  The continuous data will be summarized using the number of observations (n), arithmetic mean (mean), standard deviation (SD), median, IQR, minimum and maximum value.

  The number of observations (n) will be presented with no decimal place, Mean, median and IQR will be presented up to one decimal places from the original value, SD up to one decimal places from the mean value, minimum and maximum value as an original value.

- For categorical data

  The categorical variables will be summarized using the frequency count (n) and percentage (%) for each possible value. The frequencies will be presented up to no decimal places and percentage up to 1 decimal place.

2.1.1 General definitions

2.1.1.1 Baseline definition

Non-missing values collected at immediately prior to the first dose of study drug administration will be considered as baseline values.

Or

Baseline is defined as the pre-dose assessment on C1D1 before study treatment administration. The assessments at unscheduled visits will also be considered for the baseline computations if it is collected prior to study treatment initiation.

2.1.1.2 Handling of Missing Data

As this is Phase IV non comparative study and primary endpoint is to estimate safety, missing data will not be imputed. All Subjects observed cases will be used for analysis. Missing data will not be imputed. Only data recorded in the CRF will be analyzed.
All missing data or partial dates will be presented in the subject data listing, as they are recorded on the Case Report Form (CRF). Missing data will not be estimated or carried forward in any statistical analysis.

2.1.1.3 Pooling of Centers

Data of all Centers will be pooled together for final statistical analysis.

Enrolled Population: The participants who signed the ICF and also met the study specified eligibility criteria are generally considered as Enrolled Population.

2.2 Analysis sets

2.2.1 Safety Population

The safety set includes all Subjects who received at least one dose of capmatinib. All safety data will be analyzed using the Safety Population.

2.2.2 Full Analysis Set

The full analysis set (FAS) includes all Subjects who receive at least one dose of capmatinib and have an adequate tumor assessment as per RECIST 1.1 at baseline and have a valid follow-up assessment available. FAS will be used for all secondary analyses, unless otherwise specified.

2.2.3 Subgroup of interest

A Subgroup analysis will be performed for primary endpoint as well as efficacy endpoint with subgroup of treatment naïve vs. prior treated patients.

Treatment Naïve: Treatment naïve subjects are the subjects who have not experienced chemotherapy or radiotherapy for NSCLC before entering the study.

Prior treated patients: These are the subjects who have experienced chemotherapy or radiotherapy for NSCLC before entering the study

2.3 Patient disposition, demographics and other baseline characteristics

2.3.1 Patient disposition

Disposition of Subjects:

The following data on subject disposition will be summarized for all enrolled subjects:

- Number of subjects screened (i.e. who provided informed consent)
- Number of screen failures
- Reason for Screen Failures
  - Subject did not met Incl criteria/ met Excl criteria
  - Adverse Event
  - Death
  - Withdrawn by Subject
  - Lost to Follow-up
  - Physician Decision
  - Pregnancy
  - Other
  - If Other, specify
- Number of subjects enrolled
- Number of subjects in Safety Population
- Number of subjects in Full analysis set (FAS) population
- Number of subjects who completed the study
- Number of subjects who Early terminated the study

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Early terminated subjects are defined as and when the subjects permanently stops receiving the study treatment for any reason (prior to the planned completion of study drug administration, if any) referred from glossary table of study protocol.

- Primary Reasons for Early termination
  - Consent Withdrawn
  - Pregnancy
  - Adverse events
  - Progressive disease
  - Death
  - Lost to follow-up
  - Protocol deviation/violation
  - Any laboratory abnormalities
  - Other
  - If Other, specify

Subject data listings will be provided by all enrolled subjects.

2.3.2 Demographics and other baseline characteristics

The following patient demographics will be summarized for Safety Analysis Set population:

- Age (years)
- Gender
  - Male
  - Female
- Female of Child Bearing Potential

- Yes
- No

- Ethnicity
  - Caucasian
  - Hispanic
  - Black
  - Asian
  - Unknown
  - Other
- Race
  - Asian
  - Other
- Histological types
  - Adenocarcinoma
  - Squamous cell carcinoma
  - Large cell carcinoma
- TNM Staging for Lung Cancer
  - Stage IIIa
  - Stage IIIb
  - Stage IIIc
  - Stage IV
- Presence of bone metastases
  - Yes

- No

- Serum Pregnancy Test
  - Positive
  - Negative

Subject data listings will be provided.

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

2.4.1 Study treatment / compliance

Descriptive statistical summaries will be provided for the following variables:

- Overall Study duration

  The parameter will be summarized using descriptive statistics (n, mean, SD, median (IQR) and min - max) for safety population:

  Study duration (days) = (Date of study termination/completion - Date of obtaining ICF) +1

- Duration of Exposure

  Duration of exposure to capmatinib is the duration of exposure defined as the time between the first and last dose of treatment and will be summarized using descriptive statistics (n, mean, SD, median (IQR) and min - max) for safety population.

  Duration of exposure (days) = last date of study drug − first date of study drug + 1 (periods of interruption are not excluded).

- Actual Treatment Duration

  Actual treatment duration will be defined as overall treatment duration minus the number of days between first day and last day of intake where the subject did not take study drug, which means actual treatment duration is given by the sum of days with actual study drug intake, and will be summarized using descriptive statistics (n, mean, SD, median (IQR) and min - max) for safety population.

  Actual treatment duration = sum of days with actual study drug intake > 0.

- Drug Exposure Until the First Occurrence of AE

  Drug Exposure Until the First Occurrence of AE=Start date of first occurrence of any AE-start date of treatment +1 and will be summarized using descriptive statistics (n, mean, SD, median (IQR) and min - max) for safety population.

- Number of Cycles

  The number of subjects who are receiving the treatment will be summarized at each cycle of scheduled treatment duration of 6 months (24 weeks) using descriptive statistics (n, mean, SD, median, IQR and min - max) for safety population. Categories as cycles 1, cycle 2, cycle 3, cycle 4, cycle 5, cycle 6, cycle 7, cycle 8 and EOT will be summarized by number and percentage of subjects.

- Average Daily Dose

  The total amount of a drug actually received by a subject per day, **summed over the entire treatment period** during the study.

  Average Daily Dose= sum of (Number of treatment days × Daily dose actually received)/ Actual study duration (in days), where doses are 400mg, 300mg or 200mg

  Average daily dose will be summarized using descriptive statistics (n, mean, SD, median (IQR) and min - max) for safety population.

- Dose Reduction

  Dose reduction will be summarized by number and percentage of subjects who got recommended dose reduction from 400mg to 300mg and/or 300mg to 200mg for the first time within each category during the study.

- Number of Dose Reduced

  Number of dose reduction is summarized for number of times dose reduced per subject during the study. Number and percentage of subjects will be provided for number of times dose reduced i.e. 2,1,0.

- Compliance:

  The parameter will be summarized using descriptive statistics (n, mean, SD, median, IQR and min - max) for safety population.

  Compliance = (Total doses consumed / Total doses advised) x 100%.

- Adjusted Compliance:

  Adjusted Compliance = [{Total doses consumed / (Total doses advised – Doses omitted or reduced due to toxicity)} × 100]

Total Doses Advised is the planned or advised doses over the study period, considering the original treatment schedule.

Account for Interruptions:

- Doses Consumed : Track the total doses actually administered or consumed.
- Doses Omitted or Reduced: Document any doses that were omitted or adjusted due to toxicity.

- Any Dose Modification

  Dose modification during the study will be summarised by number and percentage of subjects in Safety population.

  Additionally, number and percentage of subjects will be presented for dose reduction, temporary interruptions, permanent drug withdrawn, dose titration, other, and if other, specify as recorded in CRF.

- Reason for Dose Modifications

  Number and percentage of subject will be presented for Adverse Event, Other, and if Other, specify under Reason for Dose Modification category as per CRF.

- Dose intensity (mg/day)

  Dose Intensity: It is computed as the ratio of total dose received and actual duration, and will be summarized using descriptive statistics (n, mean, SD, median (IQR) and min - max) for safety population.

  where Actual Duration = [(Last dose date – First dose date) + 1] (periods of interruption are excluded)

- Relative dose intensity (%)

  Relative dose intensity: It is computed as the ratio of dose intensity and planned dose intensity (i.e. planned dose received/planned duration), and will be summarized using descriptive statistics (n, mean, SD, median (IQR) and min - max) for safety population..

Subject data listings will be provided for safety population

2.4.2 Prior, concomitant and post therapies

2.4.2.1 Medical History

Medical and surgical history and current medical conditions will be recorded at the Screening Visit as designated in the Schedule of Procedures. All medical and surgical history must be noted in the Medical History and Current Medical Conditions eCRF. Relevant medical/surgical

history will be recorded at the Screening Visit from subjects' medical records and records from the investigator's interviews.

Medical history events will be coded using Medical Dictionary for Regulatory Affairs (MedDRA) dictionary version 26.1 or higher. The frequency count (n) and percentage (%) of subjects will be summarized according to the coded terms of system organ class (SOC) and preferred term (PT) with past and concurrent medications in separate tables for the safety population.

Summaries will be sorted by descending overall counts of system organ class and preferred term within system organ class and, in case of equal counts, alphabetically by system organ class and by preferred term within system organ class.

Subjects will be counted only once for each system organ class and preferred term.

Subject data listings will be provided for safety population

2.4.2.2 Prior and Concomitant Medication

Medications other than study drug, if taken and stopped within 28 days before the first study drug administration in the study are defined as prior medications. Prior medications will be documented at screening visit.

All medications (excluding study treatment and prior antineoplastic treatments), blood transfusions, surgeries and procedures (including physical therapy) administered within 28 days prior to the first dose administration of study drug through 30 days after the last dose of study drug will be recorded in the Concomitant Medications or Non-Drug Therapies and Procedures electronic case report form (eCRF), respectively.

Prior and concomitant medications will be coded using World Health Organization Drug Dictionary (WHODD) Global B3 format September 2023 which employs the Anatomical Therapeutic Chemical (ATC) classification system. For all prior medications, counts (n) & percentages (%) of subjects will be presented by ATC main group and preferred drug name/verbatim terms and will be sorted in descending order of frequency of ATC main group, preferred term within ATC main group in total for safety population and, in case of

equal counts, alphabetically by ATC main group, preferred term within ATC main group. Subjects with more than one medication of the same verbatim term will be counted only once.

Summary of Prior Radiotherapy Therapy will be presented using number and percentage of subject for Any Prior Therapy categorised under "Yes" and "No" as per CRF.

Summary of Prior Antineoplastic Medications will be provided.

Listing will be provided for Prior and Concomitant Non-Drug Treatment separately for safety population.

2.5 Analysis supporting primary objective(s)

The primary objective will be to assess the safety of capmatinib.

2.5.1 Primary endpoint(s)

The primary endpoints are:

- Incidence of AEs, including SAEs after treatment initiation, changes in laboratory values, vital signs and ECGs.
- Tolerability: dose interruptions, reductions, and dose intensity.

2.5.2 Statistical hypothesis, model, and method of analysis

The primary analysis will be to summarize the AEs, including SAEs after treatment initiation, dose interruptions, reductions, and dose intensity descriptively.

Primary analysis will be performed on the safety set as safety is the primary endpoint. Summary tables for AEs will include only AEs observed during the on treatment period.

On-treatment period is defined from day of first dose of study medication to 30 days after last dose of study medication.

An "**Overall Summary of Subjects with On Treatment Period AEs and Frequency of AEs**" will be presented with number and percentage of Subjects with corresponding two-sided exact 95% CI using Clopper and Pearson method and number of AEs in the Safety Population according to the following characteristics:

- Subjects with at least one AEs
- Subjects with at least one AEs by CTCAE Grade
    - Grade 1
    - Grade 2
    - Grade 3
    - Grade 4
    - Grade 5
- Subjects with at least one serious AEs
    - Fatal
    - Life-threatening
    - Death
    - Results in persistent or significant disability/incapacity
    - Constitutes a congenital anomaly/birth defect
    - Requires inpatient hospitalization or prolongation of existing hospitalization
    - medically significant
        - medically significant, Specify
- Subjects with at least one AEs by relationship to Study Agent
    - Related
    - Not Related
    - Not Assessable
- Subject with at least one AEs leading to below Action Taken with Study Treatment
    - Dose continued unchanged
    - Dose reduced/increased
    - Drug interrupted/permanently discontinued
    - Study Drug withdrawn
    - Unknown
- Subject with at least one AEs leading to below Outcome
    - Not recovered / Not resolved / Unchanged
    - Condition deteriorating
    - Recovered / resolved
    - Improving / recovering / resolving

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- Recovered with sequelae
- Fatal
- Unknown

2.5.3 Handling of intercurrent events

Not Applicable

2.5.4 Handling of missing values not related to intercurrent event

As this is Phase IV non comparative study and primary endpoint is to estimate safety, missing data will not be imputed. All patients observed cases will be used for analysis.

2.5.5 Sensitivity analyses

Not Applicable

2.5.6 Supplementary analyses

Not Applicable

2.6 Analysis supporting secondary objectives

All secondary analyses will be performed on the FAS, unless otherwise specified. The secondary objective is to assess the efficacy of capmatinib.

2.6.1 Secondary endpoint(s)

All assessed per RECIST 1.1 by investigator assessment

- ORR (CR+PR)
- OIRR (CR+PR) of lesions in the brain for patients who had measurable disease in the brain at baseline
- DOR calculated as the time from the date of the first documented CR or PR per RECIST 1.1 to the first documented progression or death due to any cause for patients with PR or CR
- TTR calculated as the time from first dose of capmatinib to first documented response (CR+PR) for patients with PR or CR

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- DCR calculated as the proportion of patients with best overall response of CR, PR, or SD
- PFS defined as time from first dose of capmatinib to progression or death due to any cause

2.6.2 Statistical hypothesis, model, and method of analysis

- **Overall Response Rate (ORR):-**

Overall Response Rate (ORR) is defined as the proportion of subjects with confirmed best overall response of complete response (CR) or partial response (PR), as per RECIST 1.1

The ORR will be estimated and Two-sided 95% CI is constructed using the binomial exact Clopper-Pearson method for single proportion will be provided for overall Subjects.

- **Overall Intracranial Response Rate (OIRR):-**

Overall Intracranial Response Rate (OIRR) calculated as the ORR (CR+PR) of lesions in the brain for patients who had measurable disease in the brain at baseline, as per RECIST 1.1

The OIRR will be summarized using count (n) and percentage (%) values and Two-sided 95% CI is constructed using the binomial exact Clopper-Pearson method for single proportion will be provided for patients who had measurable disease in the brain at baseline.

- **Duration of Response (DOR):-**

Duration of Response (DOR) is defined as the time from first documented response of CR or PR to date of first documented progression or death as per RECIST 1.1 criteria.

Duration of Response will be summarized using median as DOR (in months) with 95% CI, 25th and 75th percentiles and Kaplan-Meier estimated probabilities with corresponding 95% CIs at different time points.

Followings are the definition for the Event and Censored:-

Event: Disease progression or Death due to any cause for patients with PR or CR

Censored: Subjects continuing with CR or PR without disease progression or Death.

Duration of treatment response (days) = Date of disease progression or Death - date of first assessment of response based on Imaging + 1.

For censored subjects, the treatment response (days) = Last date known to be progression-free - date of first assessment of response based on Imaging + 1

- **Time To response (TTR):-**

Time To response (TTR) is defined as duration of time between the date of first dose of capmatinib and the date of first documented response of either CR or PR as per RECIST 1.1 criteria.

Time To response (TTR) will be summarized using median as TTR (in months) with 95% CI, 25th and 75th percentiles and Kaplan-Meier estimated probabilities with corresponding 95% CIs at different time points.

Followings are the definition for the Event and Censored:-

Event: Subjects who have Objective response (CR or PR).

Censored: Subjects who did not experience Objective response (CR or PR) criteria before the end of the study

Time to response (Days) = [Date of first Objective response (CR or PR) – Date of first study dose] +1

- **Disease Control Rate (DCR):-**

Disease Control Rate (DCR) is defined as the proportion of patients with best overall response of CR or PR or subjects with stable disease(SD) as per investigator according to RECIST 1.1 criteria.

Disease Control Rate will be estimated and Two-sided 95% CI is constructed using the binomial exact Clopper-Pearson method for single proportion will be provided for overall Subjects.

- **Progression Free Survival (PFS) :-**

Progression Free Survival (PFS) is defined as the time from first dose of capmatinib to the date of the first documented radiological progression as per RECIST 1.1 response criteria or death due to any cause.

Clinical deterioration will not be considered as a qualifying event for progression. The PFS will be censored at the last adequate tumor assessment if one of the following occurs: absence of event; the event occurred after a new anticancer therapy is given; the event occurred after two or more missing tumor assessments.

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

A **Subgroup analysis** will be performed for primary endpoint as well as efficacy endpoint with subgroup of treatment naïve vs. prior treated Subjects.

Subject data listings will be provided for FAS population.

Followings are the definition for the Event and Censored:-

Event:

- Disease progression or death from any cause.
- Clinical deterioration will not be considered as a qualifying event for progression

Censored:

- If a patient has not progressed or is not known to have died at the date of analysis cut-off or has received any further anticancer therapy, PFS will be censored at the date of the last adequate tumor evaluation before the cut-off date or before the start of the new anticancer therapy date, whichever is earlier.
- The PFS will be censored at the last adequate tumor assessment if one of the following occurs:
    1. Absence of event, **Censor at the date of the last adequate tumor assessment** where the subject was known to be progression-free.
    2. The event occurred after a new anticancer therapy is given, **Censor at the last adequate tumor assessment prior** to the start of the new anti-cancer therapy

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3. The event occurred after two or more missing tumor assessments, the subject will be **censored at the date of the last adequate tumor assessment** before the missing assessments.

PFS time (days) = Date of disease progression or death - date of enrollement+1

- **Duration of exposure**

Duration of exposure is the duration of exposure defined as the time between the first and last dose of treatment

Duration of exposure to capmatinib will be summarized using descriptive statistics (n, mean, SD, median and min - max) for Safety Analysis population

Duration of exposure (days) = last date of study drug − first date of study drug + 1 (periods of interruption are not excluded).

2.6.3 Handling of intercurrent events

Not Applicable

2.6.4 Handling of missing values not related to intercurrent event

Not Applicable

2.6.5 Sensitivity analyses

Not Applicable

2.6.6 Supplementary analyses

Not Applicable

2.7 Safety analyses

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

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

- Pre-treatment period: from day of patient's informed consent to the day before first dose of study medication
- On-treatment period: from day of first dose of study medication to 30 days after last dose of study medication

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- Post-treatment period: starting at Day 31 after last dose of study treatment. The safety summary tables will include only data collected during the on-treatment period. However, all safety data will be listed with data collected during the pre-treatment and post treatment period flagged

2.7.1 Adverse events (AEs)

An AE is any untoward medical occurrence (e.g., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a clinical investigation patient after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

The investigator has the responsibility for managing the safety of individual patient and identifying AE.

Novartis qualified medical personnel will be readily available to advise on trial related medical questions or problems.

Patients whose MET exon 14 skipping mutation positive status is known will sign the main study ICF.

The occurrence of AEs must be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination findings, laboratory test findings, or other assessments.

Adverse events which will be counted for a specific treatment period are those which are treatment-emergent. These events are those with an onset after the start of the treatment period, or which were present prior to the start of the treatment period but increased in severity, changed from being not suspected to being suspected of study treatment relationship, or developed into SAEs after the start of the treatment period.

Summary tables for AEs will include only AEs observed during the on treatment period. However, all safety data (including those from the pre and post-treatment periods) will be listed and those collected during the pre-treatment and after the on-treatment period will be flagged. The incidence of treatment-emergent AEs (new or worsening from baseline) will be summarized by system organ class and/ or preferred term, severity (based on CTCAE grades), type of AE, and relation to study treatment. Deaths reportable as SAEs and non-fatal SAEs will be listed by patient and tabulated by type of AE. Specific safety event categories may be considered. Such categories consist of one or more well-defined safety events which are similar in nature and for which there is a specific clinical interest in connection with the study treatment. For each specified category, number, and percentage of patients with at least one event per category will be summarized.

A patient with multiple adverse events within a primary system organ class is only counted once towards the total of the primary system organ class.
The following summaries will be presented:

- Incidence of Subjects with at least one TEAEs by System Organ Class , Preferred Term and worst CTCAE grade
- Incidence of Subjects with at least one TEAEs by System Organ Class, CTCAE Term and worst CTCAE grade
- Overall Summary of Subjects with Serious TEAEs and Frequency of AEs
- Incidence of Subjects with at least one Serious TEAEs by System Organ Class , Preferred Term and worst CTCAE grade;
- Incidence of Subjects with at least one Serious TEAEs by System Organ Class , CTCAE Term and worst CTCAE grade;
- Incidence of Subjects with at least one TEAEs Related to Study Treatment by System Organ Class, Preferred Term and worst CTCAE grade;
- Incidence of Subjects with at least one TEAEs Related to Study Treatment by System Organ Class, CTCAE Term and worst CTCAE grade;
- Incidence of Subjects with at least one TEAEs by Action Taken with Study Treatment by System Organ Class, Preferred Term and worst CTCAE grade;
- Incidence of Subjects with at least one TEAEs by Outcomes by System Organ Class, Preferred Term and worst CTCAE grade - Safety Population
- Incidence of Subjects with at least one Serious TEAEs Leading to Death by System Organ Class, Preferred Term and worst CTCAE grade;
- Incidence of Subjects with at least one Serious TEAEs Leading to Death and Related to Study Treatment by System Organ Class, Preferred Term and worst CTCAE grade
- Incidence of Subjects with at least one TEAEs by Specific Safety Event Categories by System Organ Class, Preferred Term and worst CTCAE grade
- Incidence of Subjects with at least one TEAEs by Specific Safety Event Categories by System Organ Class, CTCAE Term and worst CTCAE grade
- Incidence of Time to First Occurrence of AE
- Incidence Of Subjects With Frequency Of Peripheral Edema and other most frequent AEs

- Listing of Adverse Events: subject ID, Adverse Event Term, CTCAE Term, System Organ Class/ Preferred Term, CTCAE grade, Start and Stop dates of study drug administration, Start and Stop date of AE, TEAE Flag, AE Observation Period Flag (Pre-Treatment/On- Treatment /post- Treatment), Seriousness

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Criteria, Relationship to Study Agent, Action Taken with Study Treatment, Outcome.

- Listing of Serious Treatment-Emergent Adverse Events: subject ID, Adverse Event Term, CTCAE Term, System Organ Class/ Preferred Term, CTCAE grade, Start and Stop dates of study drug administration, Start and Stop date of AE, Seriousness Criteria, Relationship to Study Agent, Action Taken with Study Treatment, Outcome.

The analysis of these safety parameters will be done in the Safety Population.

2.7.1.1 Adverse events of special interest / grouping of AEs

Not Applicable

2.7.2 Deaths

The following listing in the Safety Population will be provided:

- Listing of Adverse Events Leading to Death: subject ID, Adverse Event Term, CTCAE Term, System Organ Class/ Preferred Term, CTCAE grade, Start and Stop dates of study drug administration, Start and Stop date of AE, TEAE Flag, AE Observation Period Flag (Pre-Treatment/On- Treatment /post- Treatment), Seriousness Criteria, Relationship to Study Agent, Action Taken with Study Treatment, Outcome.
- Listing of Serious Treatment-Emergent Adverse Events Leading to Death: subject ID, Adverse Event Term, CTCAE Term, System Organ Class/ Preferred Term, CTCAE grade, Start and Stop dates of study drug administration, Start and Stop date of AE, Seriousness Criteria, Relationship to Study Agent, Action Taken with Study Treatment, Outcome.

2.7.3 Laboratory data

For laboratory tests covered by the CTCAE version 5.0, the study's biostatistical and reporting team will grade laboratory data accordingly. For laboratory tests covered by CTCAE, a Grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used for laboratory tests where grades are not defined by CTCAE, results will be graded by the low/normal/high classifications based on laboratory normal ranges. The following summaries will be generated separately for hematology, biochemistry, and urinary laboratory tests.

- shift tables using CTCAE grades to compare baseline to the worst on-treatment value

- for laboratory tests where CTCAE grades are not defined, shift tables using the low/normal/high/(low and high)

Clinical laboratory parameters collection plan

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, Ery. Mean Corpuscular Hemoglobin, Ery. Mean Corpuscular hemoglobin Concentration, Ery. Mean Corpuscular Volume, Platelets, Erythrocytes, Leukocytes, Erythrocyte Cell Morphology, Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils, Bands, Others
Chemistry	Albumin, ALP, ALT, AST, GGT, LDH, Bicarbonate, Calcium, Magnesium, Phosphate, Chloride, Sodium, Potassium, Creatinine Direct Bilirubin, Creatinine Clearance test, Indirect Bilirubin, Total Bilirubin, Total Cholesterol, LDL Cholesterol, HDL Cholesterol, Total Protein, Triglycerides, Urea Nitrogen or Urea, Uric Acid, Amylase, Lipase, Glucose non-fasting/fasting,
Urinalysis	General Examination: Color, PH, Specific Gravity Microscopic Examination (Reb Blood Cells, Pus cells (WBCs), Crystals, Bacteria, Epithelial cells, Occult Blood)

	Chemical Examination: Bilirubin, Blood, Glucose, Ketones, Leukocytes, Nitrite, Protein, Urobilinogen
HIV markers	HIV antibody test
Hepatitis markers	Hepatitis B Virus Surface Antigen and Hepatitis C Antibody
Pregnancy Test	Urine/Serum pregnancy test[a]

ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate transaminase; Ery=erythrocyte; GGT=gamma-glutamyl-transferase; HDL=high density lipoprotein; HIV=human immunodeficiency virus; RNA=ribonucleic acid; LDH=lactate dehydrogenase; LDL=low density lipoprotein;

[a] Serum pregnancy test should be performed at screening. During the study duration urinary pregnancy tests will be performed.

Listing of all laboratory data with values flagged to show the corresponding CTCAE grades and the classifications relative to the laboratory normal ranges will be generated.
A separate listing will display notable laboratory abnormalities (i.e., newly occurring CTCAE Grade 3 or 4 laboratory toxicities).

In addition to the above-mentioned tables and listings, other exploratory analyses, for example figures plotting time course of raw or change in laboratory tests over time or box plots might be prepared based on the requirement.

2.7.4 Other safety data

2.7.4.1 ECG and cardiac imaging data

Assessment of ECG performance status will be performed as per the assessment schedule. All ECG data (QT, RR, PR, QRS, QTcF and heart rate [HR]), will be summarized by descriptive statistics (n, mean, SD, median, minimum, maximum) for continuous data at each time point for safety population.

The count (n) and percentage (%) of subjects with normal and abnormal values (Clinically Significant or Non-clinically significant) will be presented for safety population.

Subject data listings will be provided.

2.7.4.2 Vital signs

All vital signs data (BP, temperature, and pulse), physical examination including weight, height (during screening only). Actual and change from baseline to each visit will be summarized using descriptive statistics (n, mean, SD, median, minimum, maximum) for safety population

Vital signs assessments will also be summarized categorically by response at each time point for safety population.

Subject data listings will be provided.

2.7.4.3 ECOG

Assessment of ECOG performance status will be performed as per the assessment schedule, even if study treatment is being interrupted. More frequent examinations may be performed at the investigator's discretion, if medically indicated.

ECOG Performance Status will be summarized categorically by response using frequency count (n) and percentage (%)at each time point for safety population.

Score Performance Status

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 housework, 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

Subject data listings will be provided.

2.8 Pharmacokinetic endpoints

Not Applicable

2.9 PD and PK/PD analyses

Not Applicable

2.10 Patient-reported outcomes

Not Applicable

2.11 Biomarkers

Not Applicable

2.12 Other Exploratory analyses

Not Applicable

2.13 Interim analysis

No formal interim analysis is planned for this trial. The primary and final analysis will be performed after all patients have completed 24 weeks of treatment.

3 Sample size calculation

When the sample size is 47 evaluable patients, a two-sided 95% CI for the proportion of patients with any AEs using the large sample normal approximation can be estimated at a precision of 4% (i.e., half width of 95% CI for the observed proportion). It is assumed that the proportion of patients with any AE will be 98% (considered from GEOMETRY mono-1 study where 98% patients had any grade AE across all cohorts).

Adjusting for 5% drop-out rate, a total of 50 patients are expected to be enrolled in the study.

4 Change to protocol specified analyses

Not Applicable

5 Appendix

TLF Shells

5.1 Imputation rules

Not Applicable

5.1.1 Study drug

Not Applicable

5.1.2 AEs and Concomitant medication date imputation

Imputation of start dates for AEs, and ConMeds.

Missing Element	Rule
day, month, and year	No imputation will be done for completely missing dates

day, month	• If available year = year of study treatment start date then
	  • If stop date contains a full date and stop date is earlier than study treatment start date then set start date = 01JanYYYY
	  • Else set start date = study treatment start date.
	• If available year > year of study treatment start date then 01JanYYYY
	• If available year < year of study treatment start date then 01JulYYYY

day	• If available month and year = month and year of study treatment start date then
	  • If stop date contains a full date and stop date is earlier than study treatment start date then set start date= 01MONYYYY.
	  • Else set start date = study treatment start date.
	• If available month and year > month and year of study treatment start date then 01MONYYYY
	• If available month and year < month year of study treatment start date then 15MONYYYY

Imputation of end dates for AEs, and ConMeds.

Missing Element	Rule (*=last treatment date plus 30 days not > (death date, cut-off date, withdrawal of consent date))
day, month, and year	Completely missing end dates (incl. ongoing events) will be imputed by the end date of the on-treatment period*
day, month	If partial end date contains year only, set end date = earliest of 31DecYYYY or end date of the on-treatment period *
day	If partial end date contains month and year, set end date = earliest of last day of the month or end date of the on-treatment period*

Any AEs, or ConMeds with partial/missing dates will be displayed as such in the data listings.

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Any AEs, or ConMeds which are continuing as per data cut-off will be shown as 'ongoing' rather than the end date provided.

5.1.2.1 Prior therapies date imputation

Not Applicable

5.1.2.2 Post therapies date imputation

Not Applicable

5.1.2.3 Other imputations

Not Applicable

5.2 AEs coding/grading

The CTCAE grade (Version 5.0). Adverse events will be assessed and graded according to the CTCAE Version 5.0. Grade 1 to 5 will be used to characterize the severity of the AE. For CTCAE Grade 5, determine whether Grade 5 will be used to capture death information or if instead the death information will be recorded elsewhere (e.g., on a dedicated CRF to record death).

5.3 Laboratory parameters derivations

Not Applicable

5.4 Statistical models

Not Applicable

5.4.1 Analysis supporting primary objective(s)

Please refer the section 2.5.2

5.4.2 Analysis supporting secondary objective(s)

Please refer the section 2.6.2

5.5 Rule of exclusion criteria of analysis sets

Analysis Set	Criteria that cause subjects to be excluded
FAS	With out taking at least 1 dose of any component of capmatinib and Without tumor assessment in baseline and with out valid followup assessment
SAF	With out taking at least 1 dose of any component of capmatinib

6 Reference

- Capmatinib (INC280)_eCRF_ (v_3_15Mar23)
- CINC280AIN01 (Capmatinib)_Study Protocol_Amendment 1_Version 2.0
- ICH E9(R1) Harmonized Guideline: addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials. Final version on 20 November 2019

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