NOVARTIS

Clinical Development

INC280/ Capmatinib

CINC280AUS12 / NCT04926831

Phase II trial of neoadjuvant and adjuvant capmatinib in participants with stages IB-IIIA, N2 and selected IIIB (T3N2 or T4N2) NSCLC with MET exon 14 skipping mutation or high MET amplification – Geometry-N

Statistical Analysis Plan (SAP)

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Document type: SAP Documentation

Document status: Final

Release date: 27-May-2024

Number of pages: 17

Document History – Changes compared to previous final version of SAP

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
29-Sep-2021	Prior to DB lock	Creation of first version	N/A - First version	NA
27-May-2024	Prior to DB lock	Creation of final version	Due to the limited number of patients recruited to the study. Only 4 patients enrolled in the study. [redacted]	Section2, section 3, section 4 and section 5.

Table of contents

List of abbreviations

AE	Adverse Event
AESI	Adverse Events of Special Interest
AJCC	American Joint Committee on Cancer
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
[redacted]	
b.i.d.	bis in die/twice a day
BOR	best overall response
BUN	Blood Urea Nitrogen
CI	Confidence Interval
CLIA	Clinical Laboratory Improvement Amendments
CMD	Concomitant medication
CMO&PS	Chief Medical Office and Patient Safety
CO	Country Organization
CR	Complete response
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CSR	Clinical study report
CT	Computerized Tomography
CTC	Common Terminology Criteria
DAR	Drug Administration Record
DBP	Diastolic Blood Pressure
DFS	Disease Free Survival
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EOS	End of Study
FAS	Full Analysis Set
FISH	Fluorescence in situ hybridization
GCN	Gene Copy Number
GPS	Global programming & statistical environment
h	Hour
HGF	Human Growth Factor
[redacted]	

MedDRA Medical dictionary for regulatory activities
MET Mesenchymal Epithelial Transition
METex14 MET exon 14 skipping
mg milligram(s)
mL milliliter(s)
MPR Major Pathologic Response
MRI Magnetic Resonance Imaging
NCI National Cancer Institute
NGS Next Generation Sequencing
NSCLC Non-small cell lung cancer
ORR Overall response rate
[redacted]
pCR Complete Pathologic response
PD Pharmacodynamic(s)
PDS Programming Dataset Specifications
PD Pharmacodynamic(s)
PFT Pulmonary Function Test(s)
[redacted]
PPS Per-Protocol Set
PR Partial response
PS Performance Status
PT Preferred term
QT QT interval
QTcF QT interval corrected by Fridericia's formula
RAP The Report and Analysis Plan
RECIST Response Evaluation Criteria In Solid Tumors
SAE Serious Adverse Event
SAP Statistical Analysis Plan
SAS Statistical Analysis System
SBP Systolic Blood Pressure
SD standard deviation
SOC system organ class
TEAE Treatment Emergent Adverse Events
TFLs Tables, Figures, Listings
TKI Tyrosine Kinase Inhibitor
WHO World Health Organization

1 Introduction

This statistical analysis plan (SAP) module describes the planned statistical methods for all safety and efficacy analyses to be used in Phase II clinical study CINC280AUS12. Any changes made to the statistical plan and methodology after the clinical database lock will be documented as an addendum.

Note: Due to the recruitment challenges, there are very limited patients enrolled in the study. Hence the planned summary or statistical analysis, as mentioned in the protocol (CINC280AUS12--v01-Clinical Trial Protocol-21Mar2023), will NOT be performed. However, the relevant data will be listed as captured in the database for all patients.

All the outputs will be generated using statistical software SAS® Version 9.4 or higher.

1.1 Study design

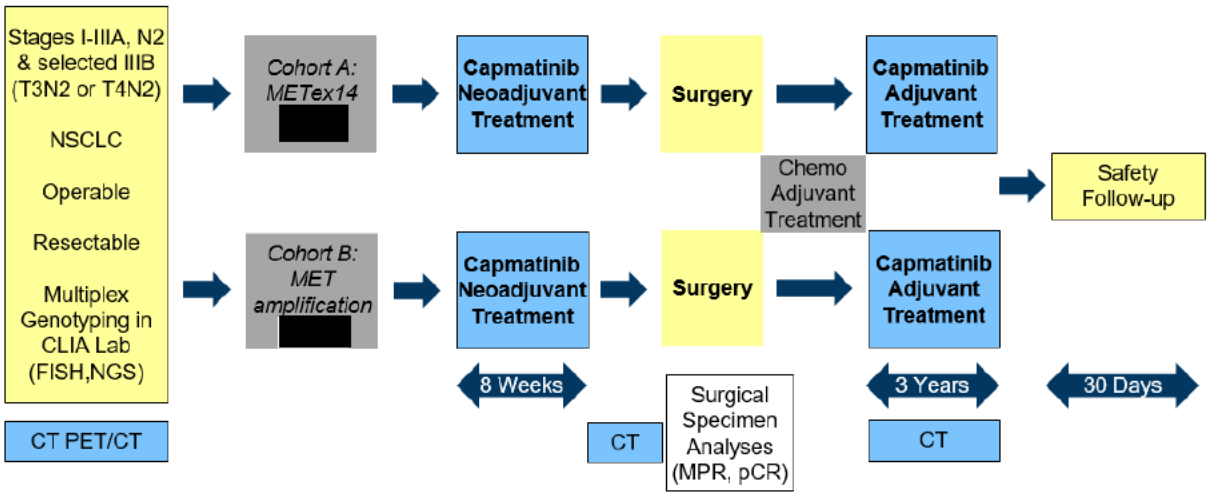
This is a Phase II, two-cohort, two-stage, study of capmatinib given for 8 weeks (2 cycles) prior to surgical resection, followed by three years capmatinib treatment in adjuvant setting. Surgery should be performed up to 2 weeks after the last dose of neoadjuvant study treatment. Please contact the sponsor if surgery will be beyond the 2-week window.

There will be 2 molecularly defined cohorts enrolling in parallel: Cohort A: MET exon 14 skipping mutations, irrespective of MET GCN or Cohort B: high level MET amplification (MET: GCN ≥10 by FISH or Foundation One CDx NGS using tumor tissue). [redacted] Participants who have both MET exon 14 skipping mutations and high-level MET amplification (MET: GCN ≥10 by FISH or Foundation One CDx NGS using tumor tissue) will be enrolled into Cohort A. An evaluable subject will undergo the neoadjuvant treatment and undergo surgery with a pathological response report analysis.

[redacted]

After surgery, participants will continue onto 3 years of adjuvant capmatinib therapy, followed by 30 days of safety follow-up.

Figure 1-1 Study design



1.2 Study objectives and endpoints

The primary, secondary [redacted] and endpoints are presented in Table 1.1.

Table 1-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
To determine the MPR in resection specimens following neoadjuvant capmatinib in 2 cohorts. Cohort A: MET exon 14 skipping mutation, irrespective of MET GCN; Cohort B: High MET amplification (MET: GCN ≥ 10)	MPR rate in each cohort based on local review, defined as the percentage of participants with ≤ 10% residual viable cancer cells
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
To assess overall response rate post neoadjuvant treatment with capmatinib in each cohort	Overall response rate (ORR) based on local investigator assessment per RECIST 1.1
To determine the complete pathologic response following neoadjuvant capmatinib therapy in each cohort	Complete pathologic response (pCR) rate based on local review
To evaluate safety and tolerability of capmatinib	Type, frequency and severity of AEs [CTCAE] v5.0), vital signs and laboratory abnormalities
To assess disease free survival with adjuvant therapy with capmatinib	Disease free survival rate at 24, 36, and 60 months
[redacted]	

Objective(s)	Endpoint(s)
[redacted]	

2 Statistical methods

2.1 Data analysis general information

The data will be analyzed by GBS, Novartis. Analysis datasets and statistical outputs will be produced using the most recent SAS® Version 9.4 (SAS Institute Inc., Cary, NC, USA), and stored in Novartis global programming & statistical environment (GPS).

It is planned that the data from all centers that participate in this protocol will be used, so that an adequate number of patients will be available for analysis.

As there are limited number of patients recruited in the study, [redacted]

2.1.1 General definitions

Study treatment

In this and subsequent analysis plan module (TFL and PDS), the terms “investigational drug”, “study drug” and “study treatment” defined as capmatinib 400 mg orally b.i.d.

Study treatment start and end date

Study treatment start date is defined as the first date when a non-zero dose of study drug is administered and recorded on the Drug Administration Record (DAR) CRF page. Similarly, study drug end date is defined as the last study drug administration date.

Study day

The study day is defined as:

•The date of the event (visit date, onset date of an event, assessment date etc.) – study reference start date + 1 if event is on or after the study treatment start date;

•The date of the event (visit date, onset date of an event, assessment date etc.) − study reference start date if event precedes the study treatment start date.

The reference start date for safety assessments (e.g. adverse event onset, laboratory abnormality occurrence, vital sign measurement, dose interruption etc.) is the start of study treatment.

For events prior to study drug start date (e.g., time of diagnosis), study day will be negative and calculated as (event date – study drug start date). Note that study drug start date is study day 1.

Due to the study drug dosing schedule, one month will be considered as 28 days. However, for "time since event" data (e.g., medical history), one month will be considered as 365.25/12 days for events that occurred prior to study Day 1.

Baseline

Baseline (e.g. for laboratory parameters), is considered as the last available assessment or value before start of the first treatment, unless otherwise stated under the related assessment. For all relevant parameters comparisons against baseline will be presented through the report. Further, if several assessments are taken on the same day, the last assessment will be used for that time point.

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

Post Baseline assessment

A post-baseline value refers to a measurement taken in the Treatment phase from Study Day 1 onwards. For patients who discontinued study treatment, all assessments listed in End of Study (EOS) visit will be performed.

Change from baseline:

When change from baseline is of interest, the following formula will be used for each scheduled visit where baseline and post-baseline values are both available:

Change from baseline = post-baseline value – baseline value.

2.2 Analysis sets

Full Analysis Set (FAS), Safety Set, [redacted] are defined in the protocol. However, as there are limited number of patients recruited in the study, any summary or statistical analysis will NOT be performed. Relevant data will be listed for all the patients.

2.3 Patient disposition, demographics and other baseline characteristics

Demographic and other baseline data including disease characteristics will be listed for all participants enrolled in the study.

Relevant medical histories and current medical conditions at baseline will be listed as captured in the database for all participants.

2.3.1 Patient disposition

A listing for data on the final status of the patient in the study will be provided. A data listing of screened patients who did not take study drug will be also provided with reasons for screening failure.

2.3.2 Patient demographics and other baseline characteristics

Listings will be provided for demographic variables for all patients.

Data to be collected on participant characteristics at screening include:

- Other background or relevant medical history (prior antineoplastic therapies (medications, radiation, surgeries)
- Prior antineoplastic therapies (medications, radiation, surgeries).
- Other assessments to be completed for the purpose of determining eligibility (ECOG performance status, complete physical examination [only recorded in source documentation], vital signs, height, weight, hematology, blood chemistry, coagulation studies, urinalysis and 12-Lead ECG)
- Prior and current concomitant medications and surgical and medical procedures

Medical history

Medical history and current medical conditions will be listed by system organ class and preferred term of the Medical Dictionary for Drug Regulatory Affairs (MedDRA) dictionary.

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

2.4.1 Study treatment / compliance

The duration of exposure to capmatinib will be presented in days. All the dosing related data will be listed. Due to the limited number of patients recruited to the study analysis will not be performed.

2.4.2 Prior, concomitant and post therapies

Prior and concomitant medications/significant non-drug therapies will be listed in all patients.

- Prior medications are defined as treatments taken and stopped prior to first dose of study treatment.
- Concomitant medications are medications that started on or after the first dose of study drug and before 30 days after the last dose of the treatment or started before the first dose of study drug and continued after the first dose of study drug.

Listings will be provided for patients receiving prior and concomitant medication or significant non-drug therapy will be presented separately, by Anatomical Therapeutic Classification (ATC) class and preferred term.

Surgical and medical procedures will be listed by primary system organ class and MedDRA preferred term.

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 Surgical and Medical Procedures eCRF, respectively. Medications include not only physician prescribed medications, but also all over-the counter medications, herbal medications, food supplements and vitamins.

2.5 Analysis of the primary objective

2.5.1 Primary endpoint

Due to limited number of patients the primary endpoint will not be analyzed using statistical methods mentioned in the protocol. The Residual Viable Tumor assessments data (both local and central review), related to the primary endpoint will be listed for all the patients:

2.5.3 Handling of missing values/censoring/discontinuations

Not applicable.

2.5.4 Supportive analyses

Due to the limited number of patients, no statistical analysis will be performed.

2.6 Analysis of the key secondary objective

Not applicable.

2.7 Analysis of secondary efficacy objective(s)

2.7.1 Secondary endpoints

Due to limited number of patients the secondary endpoints will not be analyzed using statistical methods mentioned in the protocol.

Tumor assessment and the responses (as per investigator) will be listed.

2.7.2 Statistical hypothesis, model, and method of analysis

Due to the limited number of patients, no statistical analysis will be performed.

2.7.3 Handling of missing values/censoring/discontinuations

Not applicable.

2.8 Safety analyses

Listings will be presented for safety data, for all patients.

2.8.1 Adverse events (AEs)

Listings will be provided for AEs for all patients.

[redacted]

For clinicaltrials.gov site reporting, tables on on-treatment AE which are not serious with an incidence greater than and equal to 5%; on-treatment serious adverse events and SAE suspected to be related to study treatment will be provided by system organ class and PT.

2.8.1.1 Adverse events of special interest / grouping of AEs

Not applicable

2.8.2 Deaths

All deaths due to any reason will be taken into account at any time the death occurred.

2.8.3 Laboratory data

Grading of laboratory values will be assigned programmatically as per NCI CTCAE version 5.0. The calculation of CTCAE v 5.0 grades will be based on the observed laboratory values only, clinical assessments will not be taken into account.

CTCAE v 5.0 grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be applicable.

Listing will be generated separately for hematology and biochemistry tests.

2.8.4 Other safety data

2.8.4.1 ECG and cardiac imaging data

12- lead ECGs including RR, PR, QRS, QT, QTcF, and HR intervals will be obtained for each participant during the study. ECG data will be read and interpreted locally.

All ECG data will be listed by subject and visit.

2.8.4.2 Vital signs

Vital signs include blood pressure, pulse measurement, respiratory rate, body temperature, Height and Body weight.

Vital signs will be measured at screening and at subsequent time points. Height will be measured at screening and Body weight will be measured at screening and at subsequent time points. Listings will be presented for all patients.

2.8.4.3 ECOG performance status

The Eastern Cooperative Oncology Group (ECOG) performance status will be assessed according to the PS scale as specified in the table below.

Grade	ECOG 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 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

2.8.4.4 Pregnancy Test

Not applicable.

[redacted]

[redacted]

2.14 Interim analysis

Not Applicable.

[redacted]

4 Change to protocol specified analyses

The study recruitment was prematurely discontinued due to the recruitment challenges. Only 4 subjects were enrolled. Hence the planned summary or statistical analysis, as mentioned in the protocol, will NOT be performed. To clarify, no interim analysis will be performed as mentioned in the protocol. Only, relevant data will be listed for demography, baseline characteristic, safety, and efficacy variable, as captured in the database for all patients.

5 Appendix

This will be used later for drafting CSR Appendix 16.1.9.

5.1 Imputation rules

5.1.1 Study drug

Not applicable.

5.1.2 AE date imputation

5.1.2.1 AE Start Date Imputation

Not applicable.

5.1.2.2 AE End Date Imputation

Not applicable.

5.1.3 Concomitant medication date imputation

5.1.3.1 Concomitant medication start date imputation

Not applicable.

5.1.3.2 Concomitant medication end date imputation

Not applicable.

5.1.3.3 Prior therapies date imputation

Not applicable.

5.1.3.4 Post therapies date imputation

Not applicable.

5.1.3.5 Other imputations

Not applicable.

5.2 AEs coding/grading

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

The verbatim term recorded on CRF will be identified as adverse event and will be coded by primary system organ class and preferred term using MedDRA version 20.1 and above. AEs will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

5.3 Laboratory parameters derivations

Not applicable.

5.4 Statistical models

5.4.1 Primary analysis

Not applicable.

5.4.2 Key secondary analysis

Not applicable.

5.5 Rule of exclusion criteria of analysis sets

Not applicable.

6 Reference

1. CINC280AUS12--v01-Clinical Trial Protocol_21Mar2023