NOVARTIS

Clinical Development

INC280

CINC280X2201 / NCT01737827

A Phase II, open label, single arm, multi-center study of INC280 administered orally in adult patients with advanced hepatocellular carcinoma

Statistical Analysis Plan (SAP)

Author: [redacted] Trial Statistician

Document type: SAP Documentation

Document status: Final Amendment 01

Release date: 28-Nov-2022

Number of pages: 26

Document History – Changes compared to previous version of SAP

Version	Date	Changes
0.1	08-Dec-2016	Create
1.0	18-Jan-2017	Final version after CTT review
2.0	28-Nov-2022	Updated to align with the Protocol amendment V6.0

Table of contents

1 Introduction

This Statistical Analysis Plan (SAP) provides detailed statistical methodology for the analysis of data from study CINC280X2201 that will be presented in the Clinical Study Report (CSR). The output shells (in-text and post-text) accompanying this document can be found in the TFL shells document. The specifications for derived variable and datasets can be found in the Programming Datasets Specifications (PDS) document.

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

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

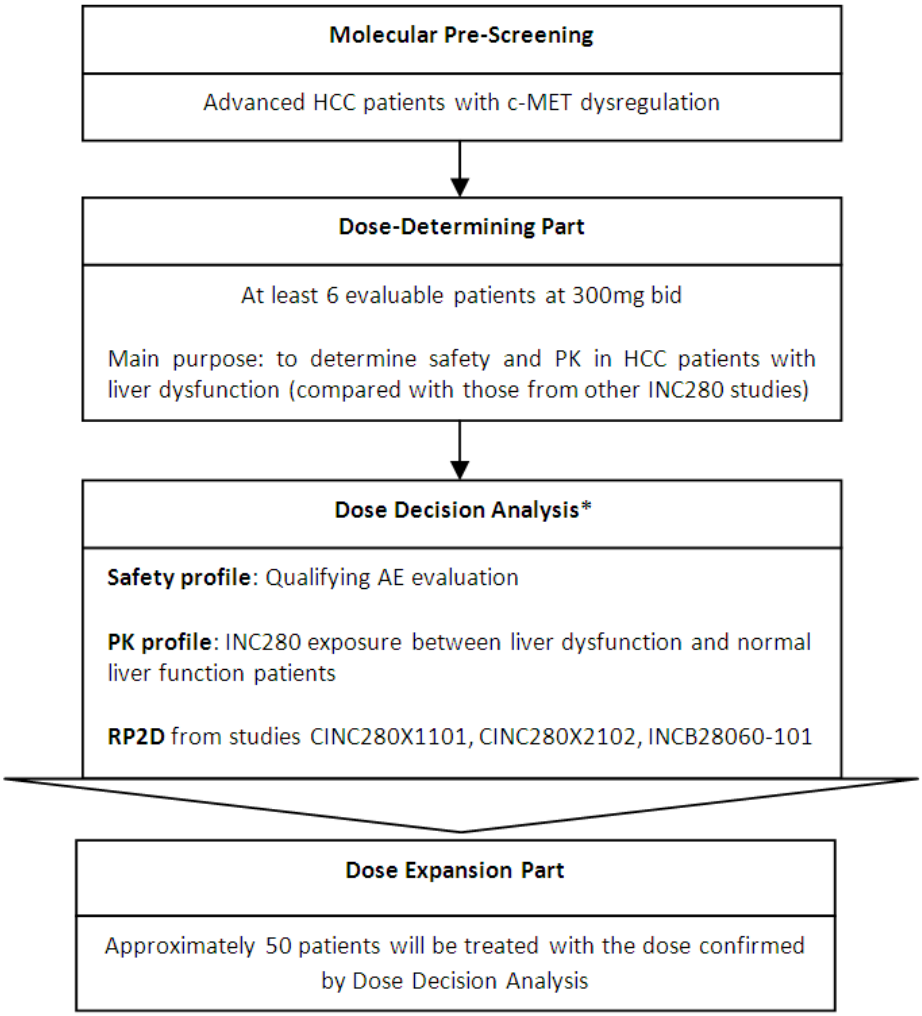
As Novartis decided to halt the enrollment in the expansion part in December 2016 (enrollment halt letter to investigators on 24-Nov-2016), the enrollment to the expansion part was permanently halted after 25-Dec-2016 (no patients will be enrolled beyond 25-Dec-2016), the study data will be analyzed and reported based on all data in the final Clinical Study Report (CSR).

The content of this SAP is based on protocol CINC280X2201 version 6.0.

1.1 Study design

This is a Phase II, open label, single arm, multicenter study of INC280 administered orally as first-line treatment in adult patients with advanced hepatocellular carcinoma (HCC). Patients will be enrolled into the study in 2 parts (Dose-Determining and Dose Expansion parts) where the first part will allow the assessment of safety and PK profiles prior to initiating a larger second part.

During the Dose-Determining Part, at least six patients will be enrolled and treated with INC280 at 300 mg bid in capsule formulation. The dose for the Dose Expansion Part will be determined after the Dose-Determining Part.



*The rules for dose recommendation for the Dose Expansion Part will be followed as listed in Table 6-1

1.2 Study objectives and endpoints

Objectives and related endpoints are described in Table 1-1 below. Planned objectives and endpoints which will not be considered for analysis in the full CSR are noted in the table below.

Table 1-1 Objectives and related endpoints

Objective	Endpoint	Analysis
Primary		
To estimate overall clinical activity of INC280 in advanced HCC patients with c-MET dysregulation.	Time to progression (TTP) assessed using RECIST version 1.1	Section 2.7
Secondary		
To further assess the clinical activity of INC280 in advanced HCC patients with c-MET dysregulation	Overall Response Rate (ORR), Progression Free Survival (PFS), Overall Survival (OS) and Disease Control Rate (DCR)	Section 2.8
To characterize the safety and tolerability of INC280 in advanced HCC patients.	**Safety:** Adverse Events (AEs), serious AEs (SAEs), changes in hematology and chemistry values, vital signs, electrocardiograms (ECGs) **Tolerability:** Dose interruptions, reductions and dose intensity	Section 2.9
To characterize the pharmacokinetics (PK) of INC280 in patients with advanced HCC.	Plasma concentration vs. time profiles, plasma PK parameters including but not limited to AUC0-t, AUCinf, Cmax and Tmax	Section 2.10

2 Statistical Methods

2.1 Data analysis general information

The data will be analyzed by Novartis personnel and/or designated CRO(s) using SAS version 9.4, and for Bayesian modeling, R version 2.13.2 and Winbugs 1.4.3. PK parameters will be calculated using non-compartmental methods available in Phoenix WinNonlin version 6.4 or above.

The data will be summarized with respect to demographic and baseline characteristics, efficacy observations and measurements, safety observations and measurements, and all relevant PK using descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) for quantitative data and contingency tables (frequencies and percentages) for qualitative data.

Demographic and safety data will be summarized and listed by study treatment groups.

Study treatment groups refer to

- INC280 300 mg BID Capsule
- INC280 600 mg BID Capsule
- INC280 400 mg BID Tablet

Analyses of efficacy data may be summarized by study parts and revised definition of c-MET positivity, as introduced in Protocol Amendment 2; i.e. MET gene copy number ≥5 by FISH with c-MET IHC intensity score 2+ in ≥50% of tumor cells or unknown, or c-MET IHC intensity score 3+ in ≥50% of tumor cell, or presence of c-MET mutation:

- Dose Determining
- Dose Expansion
    - c-MET high
    - c-MET low

The cMET IHC and FISH analyses were performed through Novartis designated central laboratories.
All data collected for patients in the Dose-Determining part will be reported at the initial Dose-Determining dose level, irrespective of whether a patient undergoes intra-patient escalation to a higher dose level.
The statistical analyses will take into account the study treatment formulation as appropriate.
The primary and secondary endpoints (refer to Section 1.2) will be performed based on FAS. For more information please refer to Section 2.7.1.

2.1.1 General definitions

Study drug and study treatment

Both **study drug** and **study treatment** refer to the study compound: INC280.

Date of first administration of study treatment

The date of first administration of study treatment is derived as the first date when a non-zero dose of study treatment was administered as per the Dosage Administration eCRF.

Date of last administration of study treatment

The date of last administration of study treatment is derived as the last date when a nonzero dose of study treatment was administered as per the Dosage Administration eCRF.

Study day

The study day for safety and efficacy assessments will be calculated as the difference between the date of the event (onset date of an event, assessment date etc.) and the start of study treatment plus 1. The first day of study treatment is therefore study Day 1. Example: if start of study treatment is on 05-Jan-2014 and start date of an adverse event is on 09-Jan-2014 then the study day of the adverse event onset is 5. For safety assessments before start of study treatment, the study day is negative and derived by (date of event - start date of study treatment). For example: if start of study treatment is on 05-Jan-2014 and date of lab measurement is on 02-Jan-2014 then the study day of the laboratory abnormality is -3. Note, the day of start of study treatment is Day 1, and the day before the date of first study treatment is Day - 1, not day 0.

Baseline

Baseline is the result of an investigation describing the "true" state of the patient before start of study treatment administration.

For safety and efficacy evaluations, the last available assessment on or before the date of start of study treatment is taken as "baseline" assessment. In case time of assessment and time of treatment start is captured, the last available assessment before the treatment start date/time is used for baseline.

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

On-treatment assessment/event observation periods

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

1. ***pre-treatment period***: from day of patient's first informed consent to the day before first administration of study treatment
2. ***on-treatment period***: from date of first administration of study treatment to 30 days after date of last actual administration of any study treatment (including start and stop date)
3. ***post-treatment period***: starting at day 30+1 after last administration of study treatment.

Safety summaries 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 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).

However, all safety AE data (including those from the pre-treatment period) will be listed.

2.2 Analysis sets

Full Analysis Set

The Full Analysis Set (FAS) comprises all patients who received at least one dose of INC280. The FAS will be used for all listings of raw data. Unless otherwise specified the FAS will be the default analysis set used for all analyses.

Safety Set

The Safety Set includes all patients from the FAS who have received at least one dose of INC280 and had at least one valid post-baseline safety assessment.

Please note: A **"no"** to indicate that the patient had no AEs (on the AE eCRF) constitutes a valid safety assessment.

Per-protocol Set

Not applicable. As the study did not meet the planned enrollment, supportive analysis with PPS is no longer of clinical interest.

Dose-determining analysis set

The dose-determining set (DDS) consists of all patients from the safety set (who are in the Dose-Determining Part) who either meet the minimum exposure criterion and have sufficient safety evaluations (as determined by the Investigators and Novartis), or who have experienced a qualifying AE during the first four weeks of treatment.

A patient is considered to have met the minimum exposure criterion at a dose level if they receive INC280 at the planned dose, BID for at least 21 days within the first four weeks of treatment (≥75% planned administration). Patients who do not experience a qualifying AE during the first four weeks are considered to have sufficient safety evaluations if they have been observed for ≥28 days following the first dose, and are considered by both the Sponsor and Investigators to have enough safety data to conclude that a qualifying AE did not occur.

Pharmacokinetic analysis set

The pharmacokinetic analysis set (PAS) consists of all patients who provide an evaluable PK profile. A profile is considered evaluable if all of the following conditions are satisfied:

- Subject receives one of the planned treatments
- Subjects provides at least one primary PK parameter
- Subject did not vomit within 4 hours after the dosing of INC280

2.2.1 Subgroup of interest

Analyses of efficacy data may be presented separately for patients meeting the revised definition of c-MET positive, as introduced in Protocol Amendment 2; i.e. MET gene copy number ≥5 by FISH with c-MET IHC intensity score +2 in ≥50% of tumor cells or unknown, or c-MET IHC intensity score +3 in ≥50% of tumor cell or presence of c-MET mutation.

The primary and secondary endpoints (refer to Section 1.2) will be performed based on FAS. For more information please refer to Section 2.7.1.

2.3 Patient disposition, demographics and other baseline characteristics

Summaries and listings described in this section will be done by study treatment groups based on the FAS.

2.3.1 Patient disposition

The FAS will be used for the patient disposition summary tables and listings. The following will be tabulated:

- Number (%) of patients who are still on-treatment (based on non-completion of the 'End of Treatment Disposition' page),
- Number (%) of patients who discontinued treatment (based on completion of the 'End of Treatment Disposition' page with discontinuation date and reason entered),
- Primary reasons for study treatment discontinuation (based on discontinuation reason entered in the 'End of Treatment Disposition' page),
- Number (%) of patients who complete study evaluation (based on completion of the 'End of Post-treatment follow-up' page with discontinuation date and reason entered),
- Primary reasons for study evaluation completion (based on discontinuation reason entered in the 'End of Post-treatment follow-up' page),

Treatment/study completion status and the reason for discontinuation from study will be listed, along with dates of first and last study drug treatment, duration of exposure to study drug treatment and date of discontinuation for each patient.

2.3.2 Basic demographic, Prognostic factors for HCC and background data

Demographic data including age, sex, race, ethnicity, height, baseline weight, body mass index (BMI), ECOG(WHO) performance status, HBV/HCV at diagnosis, Child Pugh, alpha fetoprotein, portal vein invasion at diagnosis and distant metastases at diagnosis will be listed and summarized. In addition, child bearing potential and pregnancy test results will be listed, and age (18 - <65, 65 - <85, ≥85 years) and weight (<55, 55-<75, ≥75 kg) categories will be summarized.

BMI is calculated using the following formulas:

- BMI [kg/m2] = weight[kg] / (height[m]**2)

2.3.3 Medical History

Relevant medical history and current medical conditions will be listed using Safety set..

2.3.4 Prior antineoplastic therapy

Concomitant medications will be coded using the WHO Anatomical Therapeutic Chemical (ATC) dictionary using the latest version available prior to clinical database lock.

All concomitant medications will be listed using Safety set, with a flag to differentiate those which started more than 30 days after the last study treatment.

2.3.5 Diagnosis and extent of cancer

Diagnosis and extent of cancer will be listed, including all of the information collected in eCRF.

2.4 Protocol deviations

All protocol deviations will be finalized before database lock. For the purpose of excluding patients from the analysis sets defined in Section 2.2, the protocol deviations and non-protocol deviations and severity codes are defined in Table 2-1.

Table 2-1 Protocol deviations and non-protocol deviations

Analysis set	Protocol deviations with ID [severity codes leading to exclusion]
Full analysis set	[GCP01] The patient was enrolled and the ICF was not signed [511]
Safety set	[PROC01] Patient has had at least one dose of INC280, but has no post-baseline safety assessment [2]
Dose-determining set	[PROC04] For patients in dose-determining part: Patient did not have sufficient safety assessments by Cycle 2 Day 8 for the investigator to complete the Dose Decision Analysis [16] [PROC09] For patients in dose determining part: Patient did not receive INC280 at the planned dose, BID for at least 21 days within the first four weeks of treatment and did not experience a qualifying AE during the first four weeks [16]
Pharmacokinetic analysis set	[PROC02] Patient has no PK sample collected for INC280 [24]
Other	[COMD01] Patients participate in additional parallel investigational drug or device studies [256] [COMD02] Patient received another anticancer therapy other than the study treatments while on the study [256]
[511] exclude from all analysis [2] exclude from safety analysis [16] exclude from dose-determining set [24] exclude from dose-determining set and pharmacokinetic analysis set [256] exclude from date only	

2.5 Study treatment

Summaries and listings described in this section will be done by study treatment groups based on the Safety set.

2.5.1 Data handling

2.5.1.1 Data Imputation

The following rule should be used for the imputation of date of last administration (please refer to Sections 2.1.1) for a given study treatment:

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

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

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

Use Dec31yyyy

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

Use EOT date

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

Use last day of the Month (mm).

All other cases should be considered as a data issue and the statistician should contact the data manager of the study.

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

Use the start date of that record.

Patients with missing start dates are to be considered missing for study treatment related calculations described in Section 2.5.2 and no imputation will be made. If the date of first administration is missing, then the date of last administration should not be imputed.

2.5.2 Data analysis

Duration of exposure, actual cumulative dose, dose intensity (DI) and relative dose intensity (RDI) will be summarized for the study treatment. Duration of exposure will be categorized into time intervals; frequency counts and percentages will be presented for the number(%) of patients in each interval. The number (%) of patients who have dose reductions or interruptions, and the reasons, will be summarized by study treatment.

Patient level listings of all doses administered on treatment along with dose change reasons will be produced.

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

2.5.2.1 Duration of exposure to study treatment

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

The last date of exposure to study treatment is the last dates of exposure to INC280, i.e., a patient had a permanent discontinuation of the study drug on 06-Jan-2013 after being put on a temporary interruption since 01-Jan-2013. In this case the last date of exposure is 31-Dec-2012.

Summary of duration of exposure of study treatment will include categorical summaries (based on time intervals: <=3 weeks, 3-<=9 weeks, 9-<=18 weeks and >18 weeks) and continuous summaries (i.e. mean, standard deviation etc.) using units of days.

2.5.2.2 Cumulative dose

Cumulative dose of a study drug is defined as the total dose given during the study drug exposure and will be summarized.

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

The planned cumulative dose is the planned total daily dose * Duration of exposure to study drug (days).

The **actual cumulative dose** refers to the total actual dose administered, over the duration for which the patient is on the study treatment as documented in the Dose Administration eCRF, i.e., the actual cumulative dose is the sum of the non-zero doses recorded over the dosing period and the planned cumulative dose is the planned starting dose summed over the same dosing period.

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

2.5.2.3 Dose intensity and relative dose intensity

Dose intensity (DI) for patients with non-zero duration of exposure is defined as follows:

DI (*dosing unit / unit of time*) = Actual Cumulative dose (*dosing unit*) / Duration of exposure (*unit of time*).

For example, for INC280, the dosing unit is mg and actual cumulative dose is 1200 mg, and the unit of time is a day and duration of exposure is 18 days, then

DI (mg/day) = Actual Cumulative dose (mg) / Duration of exposure (day)

= 1200 (mg) / 18 (day) = 66.7 (mg/day)

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

Planned dose intensity (PDI) is defined as follows:

PDI (*mg / day*) = Planned Cumulative dose (*mg*) / Duration of exposure (*day*).

Relative dose intensity (RDI) is defined as follows:

RDI = DI (*mg / day*) / PDI (*mg / day*).

DI and RDI will be summarized for the study drug. The RDI will be tabulated using the following intervals: <0.5, >=0.5-<0.75,>=0.75-<0.9, >=0.9-<1.1, >=1.1.

2.5.2.4 Dose reductions, interruptions or permanent discontinuations

The number of patients who have dose reductions, permanent discontinuations or interruptions, and the reasons, will be summarized for the study drug.

'Dose interrupted', and 'Dose permanently discontinued' fields from the Dosage Administration CRF pages (DAR) will be used to determine the dose interruptions, and permanent discontinuations, respectively. Dose reductions will be derived programmatically using the dosing information as described below.

The corresponding fields 'Reason for dose change/dose interrupted' and 'Reason for permanent discontinuation' will be used to summarize the reasons.

A dose change is either 'change in prescribed dose level' or 'dosing error' where actual dose administered/total daily dose is different from the prescribed dose.

For the purpose of summarizing interruptions and reasons, in case multiple entries for interruption that are entered on consecutive days with different reasons will be counted as separate interruptions. However, if the reason is the same in this mentioned multiple entries on consecutive days, then it will be counted as one interruption.

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

2.6 Analysis of the qualifying adverse events within first four weeks of treatment for dose determination

A two-parameter Bayesian Logistic Regression Model (BLRM) guided by the Escalation with Overdose Control (EWOC) principle will be used for the safety analysis. This safety analysis (to be performed during the dose decision analysis after the Dose-Determining Part as well as to confirm the Expansion Part dose) will be based on data (occurrence/absence) of certain AEs within the first 28 days treatment. Doses available for consideration as the Expansion Part dose will be those estimated under the modeling for which the risk that the true rate of the qualifying AE in the first four weeks of treatment exceeds 33% is less than 25%.

The DDS will be used for these analyses.

The Bayesian approach requires the specification of prior distributions for the model parameters. All information currently available about the dose-AE relationships of single agent INC280 will be summarized in prior distributions. More details can be found in CINC280X2201-Protocol-Appendix 5.

Dose recommendation will be based on posterior summaries including the mean, median, standard deviation, 95%-credibility interval, and the probability that the true rate of qualifying AEs lies in one of the following categories:

- [0,16%] under-dosing
- [16%,33%] targeted toxicity
- [33%,100%] excessive toxicity

Following the principle of EWOC, at the end of Dose-Determining Part, a range of doses will be recommended for the Dose Expansion Part. The highest dose level in that dose range will be the highest dose that satisfies the overdose criterion that there is less than 25% chance of excessive toxicity. If the recommended Dose Expansion Part dose as per the PK analysis (See CINC280X2201-Protocol sections 10.5.4.1.1 and 6.2.2) is higher than the dose allowed by the BLRM, the highest dose allowed by the BLRM will be used for the Dose Expansion Part.

Summaries of the posterior distribution of rate of qualifying AEs based on the AE data from all patients in the DDS will be presented.

2.7 Analysis of the primary objective

2.7.1 Primary endpoint

The primary variable for analysis is Time to progression (TTP), as per local assessment, is defined as the time from the date of baseline evaluation to the date of the first documented radiological confirmation of disease progression or death due to underlying cancer (RECIST v1.1). If a patient has not had the event at the date of analysis cut-off or when he/she received any further anti-neoplastic therapy, TTP will be censored at the time of the last adequate assessment.

2.7.2 Statistical hypothesis, model, and method of analysis

The primary TTP analysis will include all patients in the FAS (on an Intention-to Treat (ITT) basis) with patients classified according to the treatment group they were assigned to, at baseline (Dose-Determining Part or Expansion Part dose).

For patients in the Dose-Determining Part, TTP will be listed along with overall response.

For patients treated at the Expansion Part dose, the distribution of TTP will be estimated using the Kaplan-Meier method. The number of censored patients and number of patients with the event along with the median TTP and quantiles (along with one-sided 90% confidence intervals) at 3 months, 6 months, 9 months and 1 year will be presented. Also, the reason of censoring will be summarized and listed for each patient.

2.7.3 Handling of missing values/censoring/discontinuations

If a patient has not experienced a radiological disease progression or death due to underlying cancer, TTP will be censored at the date of the last adequate tumor assessment, defined as the date the last tumor assessment with overall lesion response of CR, PR or SD which was made

before a censoring reason occurred, or the date of first dose of INC280 if no post-baseline assessments are available (See RECIST v1.1).

Other missing data will simply be noted as missing on appropriate tables/listings. The FAS will be used.

2.8 Analysis of the efficacy variables

Evaluation of anti-tumor activity will be based on local radiologic examinations of overall lesion response according to RECIST v1.1 (refer CINC280X2201-Protocol-Appendix 1). The variables used to evaluate anti-tumor activity are ORR, DCR, BOR, PFS as per RECIST v1.1 and OS. Summaries and listings described in this section will be done based on the FAS.

Individual lesion measurements, overall lesion response will be listed by patient. ORR, DCR and BOR will be summarized (Table 2-2) by study treatment group and by cMET status. Whereas PFS and OS will be summarized using Full analysis set.

Individual lesion measurements and overall response (investigator's assessment) at each assessment will be listed by patient and treatment group. BOR will be summarized for all patients by treatment group and the observed ORR will be summarized in terms of percentage rates with 95% confidence intervals for each treatment group. The Kaplan-Meier estimates of OS and PFS distribution functions will be presented graphically. The resulting median OS and median PFS and quantile estimates will be provided along with 95% confidence intervals. Rate estimates of PFS and OS (along with 95% CI) at 3 months, 6 months, 9 months and 1 year will presented, as given by the Kaplan-Meier analysis.

For treatments groups with less than 10 patients, Kaplan-Meier estimates and plots will not be presented.

Table 2-2 Analysis of the efficacy variables

Endpoint	Definition	Analysis
PFS	PFS is defined as the time from date of first study treatment intake to the date of the first radiologically documented progression or death due to any cause or initiation of new antineoplastic therapy.	The number of censored patients and number of patients with the event along with the resulting median PFS and quantile estimates will be provided along with 95% confidence intervals using Kaplan Meier method.
OS	OS is defined as the time from date of first study treatment intake to date of death due to any cause	The number of censored patients and number of patients with the event along with the resulting median OS and quantile estimates will be provided along with 95% confidence intervals using Kaplan Meier method.

BOR	The best overall response (BOR) is the best response recorded from the start of the treatment until disease progression/recurrence.	BOR will be summarized as observed proportion in each category, and corresponding 95% confidence intervals (CIs) based on the exact binomial distribution will be presented. Tumor volume best change from baseline will be presented graphically (waterfall graphs).
ORR	Proportion of patients with a best overall response of confirmed CR or PR at any time on study per RECIST.	ORR and corresponding 95% confidence intervals (CIs) based on the exact binomial distribution will be presented.
DCR	Proportion of patients with a BOR of CR, PR or SD at any time on study per RECIST.	DCR and corresponding 95% confidence intervals (CIs) based on the exact binomial distribution will be presented.

2.9 Safety analysis

Summaries and listings described in this section will be done by study treatment groups based on the Safety set.

2.9.1 Adverse events

2.9.1.1 Coding of AEs

Adverse events are coded using the Medical dictionary for regulatory activities (MedDRA) terminology. The latest available MedDRA version at the time of the analyses should be used. The MedDRA version used should be specified in the footnote of relevant tables.

2.9.1.2 Grading of AEs

AEs will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

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

2.9.1.3 AE summaries

AE summaries will include all AEs occurring during on-treatment period (Section 2.1.1). All AEs collected in the AE (e)CRF page will be listed along with the information collected on those AEs e.g. AE relationship to study drug, AE outcome etc. AEs starting during the post-treatment period will be flagged in the listings.

AEs will be summarized by number and percentage of patients having at least one AE, having at least one AE in each primary system organ class (SOC) and for each preferred term (PT) using MedDRA coding. A patient with multiple occurrences of an AE will be counted only

once in the respective AE category. A patient with multiple CTCAE grades for the same preferred term will be summarized under the maximum CTCAE grade recorded for the event. AE with missing CTCAE grade will be included in the 'All grades' column of the summary tables.

In AE summaries the SOC will be presented alphabetically and the PTs will be sorted within primary SOC in descending frequency, based on their frequency in the 'All Patients' column.

The following AE summaries will be produced by study treatment group:

- Overview of AE
- AEs regardless of study treatment relationship by SOC, PT and maximum grade
- AEs regardless of study treatment relationship by PT and maximum grade
- AEs suspected to be study treatment related by PT and maximum grade
- SAEs regardless of relationship to study treatment by PT and maximum grade
- SAEs suspected to be study treatment related by PT and maximum grade
- Summary of qualifying AE for dose decision analysis (Dose determining part only)
- AEs leading to discontinuation of study treatment regardless of relationship to study treatment by PT and maximum grade
- AEs leading to discontinuation of study treatment suspected to be study treatment related by PT and maximum grade
- AEs requiring dose adjustment/interruption by SOC, PT and maximum grade
- AEs requiring additional therapy by SOC, PT and maximum grade

Additionally, for the legal requirements of ClinicalTrials.gov and EudraCT, two required tables on on-treatment adverse events which are not serious adverse events with an incidence greater than 5% and on on-treatment serious adverse events and SAE suspected to be related to study treatment will be provided by system organ class and preferred term on the safety set population.

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

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

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

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

2.9.1.4 Adverse events of special interests

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

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

- Overview of adverse events of special interest for Capmatinib

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

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

2.9.1.5 Death

On-treatment deaths will be produced by study treatment group, SOC and PT. All deaths will be listed using safety set, post treatment deaths will be flagged.

2.9.1.6 Imputation rules for missing AE date

A missing AE start date will be imputed using the following logic matrix described in Table 2-3.

Table 2-3 Imputation rules for a partially missing AE start date

	AEM MISSING	AEM < TRTM	AEM = TRTM	AEM > TRTM
AEY MISSING	No imputation	No imputation	No imputation	No imputation
AEY < TRTY	(D)	(C)	(C)	(C)
AEY = TRTY	(B)	(C)	(B)	(A)
AEY > TRTY	(E)	(A)	(A)	(A)

AEM: Month AE started; AEY: Year AE started

TRTM: Month treatment started; TRTY: Year treatment started

Table 2-4 is the legend to the logic matrix shown in Table 2-3 and details the relationship of AE start date to study treatment start date.

Table 2-4 Imputation legend and AE/treatment start date relationship

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

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

No imputation will be performed for AE end dates.

2.9.2 Laboratory data

All laboratory values will be converted into SI units, as appropriate, and the severity grade calculated using CTCAE, version 4.03. Parameters for which a grading does not exist will be classified into low/normal/high group by means of laboratory normal ranges.
For each laboratory test (e.g. hematology, biochemistry, etc.) a listing of laboratory values will be provided by laboratory parameter, patient and treatment group. The frequency of notable lab abnormalities will be displayed by parameter, cycle and treatment group. Similarly, the frequency of all laboratory abnormalities will be displayed by parameter, worst CTCAE version 4.03 grade experienced and treatment group. A separate listing will display notable laboratory abnormalities (i.e., newly occurring CTC grade 3 or 4 laboratory toxicities).
Laboratory data will be summarized by presenting grade shift tables for those parameters for which CTCAE version 4.03 allows classification. All remaining data will be summarized by presenting shift tables based on normal ranges.

2.9.3 Vital signs, weight and physical examinations

Vital signs will be listed, notable values will be flagged, and any other information collected will be listed as appropriate.

2.9.4 Electrocardiograms

ECG will be listed, notable values will be flagged, and any other information collected will be listed as appropriate. Tolerability

Tolerability of study treatment will be assessed by summarizing the number of dose interruptions for the study drug. Reasons for dose interruption will be summarized by study drug. Cumulative dose, dose intensity and relative dose intensity of study drug (see Section 2.5.2) will be also be used to assess tolerability.

2.10 Pharmacokinetic data

All PK analyses will be performed based on the PAS. Patient data may be removed on an individual basis. Cycle 1 Day 15 pre-dose concentration may be utilized as concentration at 12 h post-dose for the calculation of AUC0-12,ss of INC280. This is based on the PK principle that, steady state concentration is assumed to be the same at the beginning and end of the dose

interval, in this case 12 h. Therefore the pre-dose value of the dosing period may be carried forward to the end of the 12 h-dosing interval and will be included in the PK merge data.

Descriptive graphical plots of mean (standard deviation) and geometric mean plasma concentration at Cycle 1 Day 15 steady-state will be generated by treatment group.

2.10.1 Dose-Determining Part

PK will be assessed for patients treated in the Dose-Determining Part on Cycle 1, Day 1 and 15. Patients with at least one evaluable full PK profile will be included in PK analysis. Summary statistics (number, arithmetic mean, median, standard deviation, coefficient of variance CV(%), geometric mean, geometric CV (%), minimum and maximum) will be presented for concentrations of INC280 by nominal time point and treatment dose. Graphics with concentration mean and standard deviation by time point and treatment dose will be presented as well.
The following PK parameters from Dose-Determining Part will be summarized:
Cycle 1, Day 1: AUC0-t, AUCinf, AUClast, Cmax, T1/2, Tlast, Tmax, CL/F, and Vz/F.
Cycle 1, Day 15: AUC0-t, AUCinf, AUClast, Cmax, T1/2, Tlast, Tmax, CL/F, Vz/F and Racc.
PK parameters other than Tmax will be summarized by number, arithmetic mean, standard deviation, CV%, median, range (minimum and maximum), geometric mean and geometric CV%. Number, median and range (minimum and maximum) will be presented for Tmax.

2.10.2 Dose Expansion Part

Summary statistics (number, arithmetic mean, median, standard deviation, CV(%),geometric mean, geometric CV (%), minimum and maximum) will be presented for concentrations of INC280 by nominal time point and treatment dose. Graphics with concentration mean and standard deviation by time point and treatment dose will be presented as well.

2.10.3 Data handling principles

Zero concentrations will not be included in the geometric mean calculation. Since Tmax is generally evaluated by a nonparametric method, median values and ranges will be given for this parameter.

Missing concentration values will be reported as is in data listings. Concentration values below Lower limit of quantitation will be handled as zero in summary statistics, and reported as is in data listings. Any missing pharmacokinetic parameter data will not be imputed.

2.11 Patient reported outcomes

Not Applicable.

[redacted]

2.13 Interim analyses

No formal interim analysis is planned. However the design in the dose determining part of the study foresees that decisions based on the current data are taken before the end of the study. More precisely, after at least six patients have been enrolled in the dose determining part, the dose for dose expansion part will be chosen depending on the observed data. Details of this procedure and the process for communication with investigators are provided in CINC280X2201-Protocol-Section 6.2.2.

3 Sample size calculation

Dose-Determining Part

It is expected that between 6 and 10 patients will be enrolled in order to obtain data on occurrence or absence (within first four weeks of treatment) of qualifying AE for at least 6 patients evaluable for the DDS.

Dose expansion Part

A total number of 50 patients are planned to be enrolled and treated in the dose expansion part. It is expected that 25 to 40 among these patients will have the c-MET high status as specified in the inclusion criteria. The following assumptions and design parameters are considered:

- in general the median TTP for patients treated with sorafenib has been established to be 2.8 months (Cheng et al 2009); for the c-MET high patients it has been estimated to be 2.2 months (Santora et al 2013)
- the required improvement to be seen on treatment with INC280 in the Dose Expansion Part is an increase in median TTP to approximately 4 months in patients with advanced HCC with high c-MET status and preserved liver function of Child Pugh class A with 5-6 point
- therefore a successful outcome will be indicated by an observed median TTP of ≥4 months, and a one-sided 90% lower confidence limit for median TTP of ≥2.2 months

- It is assumed that on average 1.5 patients are enrolled per month; the primary analysis is conducted 6 months after enrolment of the final patient
- Data is simulated from the exponential distribution with true mTTP = 2.2, 4, 5 and 6 months
- a 30% risk of loss to follow up per patient per year is assumed ; this corresponds to loss to follow up of approximately 15% patients given an assumed true mTTP = 4 months; censoring time is simulated from the exponential distribution with rate parameter = -log(1-0.30)/12

Kaplan-Maier method is used to estimate the median TTPs and provide the Brookmeyer-Crowley CIs in simulated event data. Table 3-1 presented the expected numbers of observed events at primary analysis, the probability that the observed mTTP is ≥4 months, the probability that the lower limit of one-sided 90% CI is >2.2 months provided the observed mTTP ≥4 months, and the probability of study success (i.e. the probability that the lower limit of one-sided 90% CI is >2.2 months and the observed mTTP is ≥4 months), given different true values of TTP and sample sizes. Therefore, with the planned enrollment, if the true median TTP is 6 months a successful outcome is expected with high probability. Conversely, a successful outcome is highly improbable if the true median TTP is as low as 2.2 months

Table 3-1 Design operating characteristics when the number of patients is 25, 30, 35 and 40, respectively

True TTP (months)	Expected number of observed events	P(observed mTTP ≥4m | true TTP)	P (lower CI >2.2m | observed mTTP ≥4m, true TTP)	P (lower CI >2.2m and observed mTTP ≥4m | true TTP)
N = 25				
2.2	22	0.01	0.76	0.01
4	19	0.52	0.95	0.49
5	18	0.77	0.97	0.75
6	16	0.90	0.99	0.89
N = 30				
2.2	27	0.01	0.81	0.01
4	24	0.50	0.97	0.49
5	22	0.79	0.98	0.78
6	20	0.92	0.99	0.92

True TTP (months)	Expected number of observed events	P(observed mTTP ≥4m | true TTP)	P (lower CI >2.2m | observed mTTP ≥4m, true TTP)	P (lower CI >2.2m and observed mTTP ≥4m | true TTP)
N = 35				
2.2	31	0.01	0.82	0.00
4	28	0.51	0.98	0.50
5	26	0.81	0.99	0.80
6	24	0.94	1.00	0.93
N = 40				
2.2	36	0.00	0.93	0.00
4	32	0.50	0.99	0.50
5	30	0.82	0.99	0.82
6	28	0.95	1.00	0.95

4 Change to protocol specified analyses

As Novartis decided to halt the enrollment in the expansion part in December 2016, therefore the following analyses as per protocol will not be performed due to insufficient data:

[redacted]

- The sensitivity analyses using PPS

4.1 Handling of missing and partial dates

For patients not known to have died prior to the cut-off date:

All events (e.g. AEs) that started before or on the cut-off date, and with end date missing or after the cut-off date will be reported as continuing and unresolved at the cut-off date. For these events, the end date will not be imputed.

Calculating duration of e.g. AEs and concomitant medications for patients known to have died prior to or on the cut-off date:

AEs and concomitant medications that started before or on the cut-off date, and with end date missing or after the cut-off date will have the end date imputed to the date of death. For these events, the imputed end date will not appear in the listings.

If imputation of an end date is required to calculate the duration of exposure to study treatment (a dose administration record with missing end date, or last date of study treatment is after the cut-off date), the end date will be imputed to the cut-off date. The imputed date will be displayed and flagged in the listings.

5 References

Cheng AL, et al (2009) Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomized, double-blind, placebo controlled trial. Lancet Oncol 10:25–34

Santoro A, et al (2013). Tivantinib for second-line treatment of advanced hepatocellular carcinoma: a randomised, placebo-controlled phase 2 study. Lancet Oncol 14: 55Onc

Neuenschwander, Branson, Gsponer (2008) Critical aspects of the Bayesian approach to Phase I cancer trials. Statistics in Medicine, 27:2420-2439.

Neuenschwander B, Capcun–Niggli G, Branson M et al (2010) Summarizing Historical Information on Controls in Clinical Trials. Clin Trials; 7(1): 5-18.Clopper CJ and Pearson ES (1934). The Use of Confidence or Fiducial Limits Illustrated in the Case of the Binomial. Biometrika.; 26,(4):404-13.

Kaplan, EL and Meier, P (1958). Nonparametric estimation from incomplete observations. Journal of the American Statistical Association.;53:457-81.