NOVARTIS

Clinical Development

INC280 (capmatinib), PDR001

CINC280X2108 / NCT02795429

A phase Ib/II, open-label, multi-center study of INC280 in combination with PDR001 or PDR001 single agent in advanced hepatocellular carcinoma

Statistical Analysis Plan (SAP)

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Document type: SAP Documentation

Document status: Final version 1.0, Amendment 1

Release date: 10-May-2021

Number of pages: 51

Document History – Changes compared to previous final version of SAP

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
26-Aug-2016	Prior to DB lock	Creation of final version 1.0	N/A - First version	NA
10-May-2021	Prior to DB lock	Creation of the Amendment 1 of the final version 1.0	This version will be used for the CSR	Structural update and various changes in wording, in order to align with the TCO SAP template (SAP_TCO_V3.0). Corrections and additions to reflect the latest amended protocol version (v5.0). Wording added for the managment of the COVID-19 situation.

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List of abbreviations

AE	Adverse Event
AESI	Adverse Event of Special Interest
[redacted]	[redacted]
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase/glutamic pyruvic transaminase/GPT
AST	Aspartate Aminotransferase/glutamic oxaloacetic transaminase/GOT
ATC	Anatomical Therapeutic Classification
AUC	Area Under the Curve
BDM	Biometrics and Data Managment
BID	bis in die / Twice daily
BLRM	Bayesian Logistic Regression Model
BOR	Best Overall Response
CI	Confidence Interval
CR	Complete Response
CRO	Contract Research Organization
CSR	Clinical Study report
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of Variation
DAR	Dose Administration Record
DBL	Data Base Lock
DDS	Dose-Determining Set
DI	Dose Intensity
DLT	Dose Limiting Toxicity
DMPK	Drug Metabolism & PharmacoKinetics
DOR	Duration of Overall Response
DRL	Drug Reference Listing
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EOT	End of Treatment
EWOC	Escalation with Overdose Control
FAS	Full Analysis Set
HCC	Hepatocellular Carcinoma
[redacted]	[redacted]
HGLT	High Level Group Term
HLT	High Level Term
IB	Investigator’s Brochure
[redacted]	[redacted]
IHC	Immunohistochemistry
ir-	Immune related
irRC	Immune-related Response Criteria

i.v.	Intravenous
LLOQ	Lower Limit Of Quantification
MAP	Meta-Analytic-Predictive
MedDRA	Medical Dictionary for Regulatory Activities
MTD	Maximum Tolerated Dose
NA	Not Assessed
NMQ	Novartis MedDRA Queries
ORR	Overall Response Rate
OS	Overall Survival
PAS	Pharmacokinetic Analysis Set
PD	Pharmacodynamics / Progressive Disease, depending on the context
PDI	Planned Dose Intensity
PDS	Programming Datasets Specifications
PFS	Progression-Free Survival
PK	Pharmacokinetics
PPS	Per-Protocol Set
PR	Partial Response
PT	Preferred Term
Q3W	Every 3 Weeks
RDI	Relative Dose Intensity
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic Acid
RP2D	Recommended Phase 2 Dose
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable Disease / Standard Deviation, depending on the context
SMQ	Standardized MedDRA Queries
SOC	System Organ Class
SSD	Study Specification Document
TBL	Total Bilirubin
TFL	Tables-Figures-Listings
TTP	Time to Progression
TTR	Time to Response
ULN	Upper Limit of Normal
UNK	Unknown
WBC	White Blood Cells
WHO	World Health Organization

1 Introduction

This Statistical Analysis Plan (SAP) provides detailed statistical methodology for the analysis of data from study CINC280X2108 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 Tables-Figures-Listings (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., MTD/RP2D declaration, Investigator's Brochure (IB) updates, abstracts, posters, presentations, manuscripts and management updates. Data used for these analyses will have a status aligned to the database lock guidance.

1.1 Study design

This is a phase Ib/II, open-label, multi-center study of INC280 in combination with PDR001 or PDR001 single agent in advanced hepatocellular carcinoma. Patients will be enrolled into the study in two parts, a phase Ib dose escalation part and a randomized phase II part. In the phase Ib part of the study, cohorts of patients will be treated with INC280 (orally twice daily), in combination with a fixed dose of PDR001 (intravenously every three weeks), in a dose escalation fashion until the Maximum Tolerated Dose (MTD) is reached or the Recommended Phase II Dose (RP2D) is established. The phase II part will be opened after the MTD/RP2D is declared.

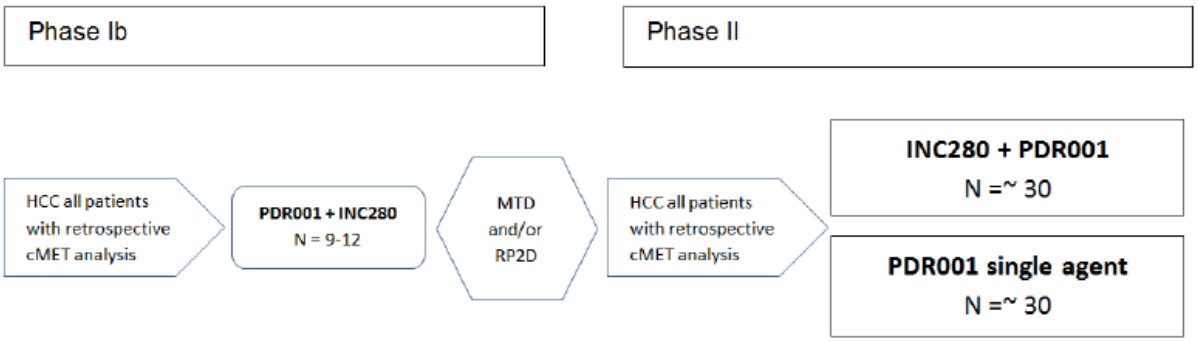
In the phase II part, approximately 60 patients will be enrolled, randomly assigned in a 1:1 ratio, to two different treatments (see Figure 1-1):

- INC280+PDR001, and
- PDR001

Randomization will be stratified by geographical region (Asian vs. non-Asian).

The study data will be analyzed and reported based on all patients' data of the dose escalation and phase II parts up to the time when all patients have potentially completed at least nine cycles of treatment or discontinued the study.

Figure 1-1 Study Design



1.2 Study objectives and endpoints

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

Table 1-1 Objectives and related endpoints

Objective	Endpoint
Primary	
Phase Ib part: To characterize the safety and tolerability of INC280 in combination with PDR001 and identify the MTD and/or RP2D	Phase Ib part: Safety: Incidence and severity of AEs and SAEs, including changes in laboratory values, vital signs and ECGs. Incidence of DLT during the first 2 cycles of treatment. Tolerability: Dose interruptions, reductions, and dose intensity
Phase II part: - To compare the efficacy of INC280 in combination with PDR001 vs. PDR001 single agent	Phase II part: Overall response rate (ORR) per Response Evaluation Criteria in Solid Tumors (RECIST v1.1)
Secondary	
Phase Ib/II part: To further characterize the efficacy of INC280 in combination with PDR001 and PDR001 single agent	Best overall response (BOR), duration of overall response (DOR), time to response (TTR), progression-free survival (PFS), time to progression (TTP), overall survival (OS), Overall response rate (ORR)
Phase II part: To characterize the safety and tolerability of INC280 in combination with PDR001 and PDR001 single agent	Safety: Incidence and severity of adverse events (AEs) and serious adverse events (SAEs), including changes in laboratory parameters, vital signs and electrocardiograms (ECGs) Tolerability: Dose interruptions, reductions and dose intensity
Phase Ib/II parts: To characterize the pharmacokinetic profile of INC280 in combination with PDR001 and PDR001 single agent	Plasma/serum PK parameters (e.g., AUC, Cmax, Tmax) Plasma/serum concentration vs. time profiles

Objective	Endpoint
Phase Ib/II parts: To assess the pharmacodynamic effect of INC280 in combination with PDR001 and PDR001 single agent	TIL characterization & CD8 and PD-L1 protein expression

2 Statistical methods

2.1 Data analysis general information

The data will be analyzed by Novartis personnel and/or designated CRO(s) using the most updated SAS version in the GPS environment, and for Bayesian modeling the most updated R and WinBUGS versions. PK parameters will be calculated using non-compartmental methods available in Phoenix WinNonlin version 5.2 or later.

The study data will be analyzed and reported (in a primary CSR if final DBL has not occurred) based on all patients' data of the dose escalation and phase II parts up to the time when all patients have potentially completed at least nine cycles of treatment or have discontinued the study. The primary CSR will include all outputs planned within the TFL shells document. Any additional data for patients continuing to receive study treatment past the data cutoff date for the primary CSR as allowed by the protocol, will be reported at completion of the study as defined in Section 4.3 of the protocol. However, only a selection of key outputs for which additional data was collected will be provided for the final report.

For each of the analyses, all statistical analyses will be performed using all data collected in the database up to the data cut-off date. All data with an assessment date or event start date (e.g. vital sign assessment date or start date of an adverse event) prior to or on the cut-off date will

be included in the analysis. Any data collected beyond the cut-off date will not be included in the analysis and will not be used for any data derivation.

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

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

General analysis conventions

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

Data will be summarized with respect to demographic and screening characteristics, efficacy and safety observations and measurements and all relevant PK and PD measurements using descriptive statistics (quantitative data) and contingency tables (qualitative data).

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

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

The following rules will be followed for reporting results unless stated otherwise:

- For the phase Ib part, cohorts treated with the same combination dose level will be pooled into a single treatment group. All summaries, listings, figures and analyses will be performed by treatment group.
- For the phase II part, all summaries, listings, figures will be presented by study arm for the efficacy analyses, and by study treatment for safety analyses. Patients from the phase II part will be classified according to the study arm to which they were assigned at baseline.

Study treatments in the phase II part:

- Treatment A: PDR001+INC280
- Treatment B: PDR001

Patients from the phase Ib dose escalation parts and the phase II part will not be pooled in any analyses unless otherwise specified.

2.1.1 General definitions

2.1.1.1 Investigational drug and study treatment

Investigational drug, will refer to the INC280 or PDR001. The terms investigational drug and study drug are used interchangeably. For consistency across studies, the term study treatment will be used throughout this document.

Investigational treatment will refer to PDR001 in combination with INC280 (i.e. PDR001+INC280) or PDR001 as single agent. The term investigational treatment may also be referred to as **study treatment**. For consistency across studies, the term study treatment will be used throughout this document.

2.1.1.2 Date of first/last administration of study treatment

The date of first (last) administration of study drug is derived as the first (last) date when a non-zero dose of any component of study treatment was administered and recorded on the Dosage Administration Record (DAR) eCRF. For the sake of simplicity, the date of first (last) administration of study treatment will also be referred as start (last) date of study treatment.

2.1.1.3 Study day

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

The study day is defined as:

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

Therefore, the first day of study treatment is study day 1.
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.

Phase Ib part

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

Phase II part

- The reference start date for safety assessments (e.g. adverse event onset, laboratory abnormality occurrence, vital sign measurement, dose interruption, pk etc.) is the start of study treatment.
- The reference start date for all other, non-safety assessments (i.e., tumor assessment, survival time, disease progression, tumor response, ECOG performance status) is the date of randomization.

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

2.1.1.4 Time unit

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

2.1.1.5 Baseline

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

Phase Ib part

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 (e.g. pre-dose ECG), the last available assessment before the treatment start date/time is used for baseline.

Phase II part

- For efficacy evaluations, the last non-missing assessment, including unscheduled assessments on or before the date of randomization is taken as "baseline" value or "baseline" assessment. In the context of baseline definition, the efficacy evaluations also include and performance status.
- For safety evaluations, the last available assessment on or before the date of start of study treatment is taken as "baseline" assessment.

For pregnancy test, baseline will be within 72 hours before first administration of study treatment.
For safety parameters (e.g. ECGs or vital signs), where study requires multiple replicates per time point, the average of these measurements would be calculated for baseline (if not already available in the database). Computation of baseline for ECG are described in Section 2.9.4.1.

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

2.1.1.6 On-treatment assessment/event and observation periods

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

1. ***pre-treatment period***: from day of patient's 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 following the last administration of study treatment.
3. ***post-treatment period***: from 31 days after date of last administration of study treatment.

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

Safety summaries (tables, figures) include only data from the on-treatment period with the exception of baseline data which will also be summarized where appropriate (e.g. change from

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

Following last administration of study treatment, AEs (including serious adverse events), and new antineoplastic therapies are collected for a period of 150 days. Following start of new antineoplastic therapy, only study treatment related AEs will be collected. However, all safety data (including those from the post-treatment period) will be listed and those collected during the pre-treatment and post-treatment period will be flagged.

2.1.1.7 Last contact date

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

Table 2-1 Last contact date data sources

Source data	Conditions
Date of Randomization	No Condition
Last known date subject alive from Survival information page	Patient status is reported to be alive, lost to follow-up or unknown.
Date of consent withdrawal	No condition
Start/End dates from concomitant medications	Non-missing medication term.
Start/End dates from further antineoplastic therapy	Non-missing medication/procedure term.
Start/End dates from dosage administration record and dosage administration record for PK	Non-missing dose. Doses of 0 are allowed.
- Tumor assessment date	Evaluation is marked as ‘done’.
Laboratory [redacted] regnancy test/PK collection dates	Sample collection marked as ‘done’/’performed’/’taken’.
Vital signs date	At least one non-missing parameter value
Performance Status date	Non-missing performance status
Start/End dates of AE	Non-missing verbatim term

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

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

2.2 Analysis Set/ Subject Classification/ Withdrawal of ICF/ Subgroups

2.2.1 Analysis sets

The number (%) of patients in each of the defined analysis set will be summarized using the FAS.

Full Analysis Set

The Full Analysis Set (FAS) comprises all patients who received at least one dose of study treatment in the phase Ib part, and all patients to whom study treatment has been assigned by randomization in the phase II part. According to the intent to treat principle, patients in the phase II part will be analyzed according to the treatment and strata they have been assigned to during the randomization procedure.

Safety Set

The Safety Set includes all patients who received at least one dose of study treatment (i.e. at least one dose of PDR001 or INC280). Patients will be classified according to treatment received, where treatment received is defined as:

- the treatment assigned if it was received at least once, or
- the first treatment received if the assigned treatment was never received.

The safety set will be the primary population for all safety related endpoints.

Per Protocol Set

The Per-Protocol Set (PPS) for the phase II part consists of a subset of FAS patients who meet the following criteria:

- Treatment according to the randomization scheme.
- Presence of at least one measurable lesion at screening according to RECIST v1.1 as per Appendix 1 of the protocol.
- Have not been previously treated with PD-1- or PD-L1-directed therapy or any therapeutic cancer vaccine.
- Histologically or cytologically documented locally advanced recurrent or metastatic HCC.
- Have received prior systemic sorafenib treatment for HCC with documented progression during or after discontinuation of sorafenib treatment, or are intolerant to sorafenib.

The PPS will be used in the phase II part of the study only and will define the patients used in the sensitivity analysis of the primary endpoint. If the PPS and the FAS are identical, then analyses described by the PPS will not be performed.

Dose-Determining Set

The Dose-Determining Set (DDS) consists of all patients in the dose escalation part who either meet the minimum exposure criterion and have sufficient safety evaluations, or have experienced a DLT during cycles 1 and 2. This constitutes an evaluable patient for the determination of MTD.

A patient is considered to have met the minimum exposure criterion if having received at least two planned doses of PDR001 and 28 days of INC280 during cycles 1 and 2. Patients who do not experience a DLT during the first two cycles are considered to have sufficient safety evaluations if they have been observed for $\geq$ 42 days following the first dose, and are considered by both Novartis and the Investigators to have enough safety data to conclude that a DLT did not occur.

Patients who do not meet these minimum dosing and safety evaluation requirements will be regarded as ineligible for the DDS and additional patients may be enrolled if required to meet the minimum cohort size for decision making, as described in Section 6.2.3 of the protocol.

Pharmacokinetic analysis set

The pharmacokinetic analysis set (PAS) consists of all patients who have at least one blood sample providing measurable INC280 and PDR001 PK data. The PAS will be used for all PK analyses.

Note: Some patients' data may not be adequate for the reliable estimation of some PK parameters. These patients will be identified at the time of the analysis and their PK parameters will be excluded from summaries.

For a concentration to be evaluable, patients are required to:

- take at least one dose of INC280 and/or PDR001
- for INC280 PK samples taken on or after Cycle 2 Day 1, take the same dose of INC280 for at least 3 consecutive days prior to sampling
- for INC280 pre-dose samples on or after Cycle 2 Day 1, do not vomit within 4 hours after the dosing of INC280 prior to sampling; for all post-dose samples, do not vomit within 4 hours after the dosing of INC280
- for pre-dose samples taken on or after Cycle 2 Day 1, have the sample collected before the next dose administration and at least 9 hours after the last dose administration of INC280

The PK parameter analysis for phase Ib part will include all patients who provide an evaluable PK profile. A profile is considered evaluable if all of the following conditions are satisfied:

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

- for Cycle 2 Day 1 profile of INC280, patient took the same dose of INC280 for at least 3 consecutive days prior to sampling
- for Cycle 2 Day 1 profile of INC280, patients are required to have the pre-dose sample collected before the next dose administration and at least 9 hours after the last dose administration of INC280.

[redacted]

2.2.2 Subject classification

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

Table 2-2 Classification based on PDs and non-PD criteria

Analysis set	Protocol deviations leading to exclusion (DVSPID)	Non protocol deviation leading to exclusion
Full analysis set	No written informed consent (OTH01, OTH02)	For Phase Ib part: No dose of study treatment (in both drugs) administered
Safety set	No written informed consent (OTH01, OTH02)	No dose of study treatment (in both drugs for the combination arm) administered
Dose-determining set	No written informed consent (OTH01, OTH02)	For Phase Ib part: • Patients had no DLT during cycles 1 and 2 and • Did not receive at least two planned doses of PDR001 and 28 days of INC280 during cycles 1 and 2. • Were not followed up for ≥ 42 days after first dose

		administration, unless patient had a DLT during this period.
Per-protocol set	• No written informed consent (OTH01, OTH02). • No presence of at least one measurable lesion at screening according to RECIST v1.1 (INCL10). • Histologically or cytologically documented type of indication different from locally advanced recurrent or metastatic HCC (INCL03). • Patients previously treated with PD-1- or PD-L1-directed therapy or any therapeutic cancer vaccine (EXCL01). • Patient received prior systemic sorafenib treatment for HCC with documented progression during or after discontinuation of sorafenib treatment, or are intolerant to sorafenib (INCL06).	For Phase II part only: • Treatment not according to the randomization scheme.
PK Analysis Set	No written informed consent (OTH01, OTH02)	No blood sample providing evaluable PK data.
[redacted]		

2.2.3 Withdrawal of Informed Consent

Any data collected in the clinical database after a patient withdraws informed consent from all further participation in the trial, will not be included in the analysis. The date on which a patient withdraws full consent is recorded in the eCRF.

Additional data for which there is a separate informed consent, e.g. PK, [redacted] etc., collected in the clinical database without having obtained that consent will not be included in the analysis. These data will be excluded by the presence of the appropriate protocol deviation criterion.

For more details on withdrawal of informed consent, please refer to Section 7.1.4 of the protocol.

2.2.4 Subgroup of interest

Not applicable.

2.3 Patient disposition, demographics and other baseline characteristics

Unless noted otherwise, summaries and listings described in this section will be based on the FAS.

2.3.1 Patient disposition

The number and percentage of the patients included in the FAS, the ones who are still on treatment at the time of the data cut-off, the ones who discontinued the study phases, as well as the reason for discontinuation will be presented.

The FAS will be used for the patient disposition summary tables and listings. The following will be tabulated overall, by treatment or study arm:

- Number (%) of patients who are still on-treatment at the time of cut-off (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 discontinued from study (based on completion of the 'End of Post Treatment Phase Disposition' page with discontinuation date and reason entered),
- Primary reasons for study evaluation completion (based on discontinuation reason entered in the 'End of Post Treatment Phase Disposition' page).

2.3.2 Demographic and other baseline characteristics

Demographic and background data including age, sex, child bearing potential, race, ethnicity, country, region, height, and baseline weight, ECOG performance status, Child-Pugh classification will be listed and summarized by treatment and study arm. Region (Asian, non-Asian) and age categories (18- <65 years, 65- < 85 years, and ≥ 85 years) will be summarized.

Additionally, information on prognostic factors as portal vein invasion and evidence of Hepatitis B and C on the patients will be presented.

2.3.3 Medical History

Medical history and current medical conditions will be coded using the latest Medical Dictionary for Regulatory Activities (MedDRA) terminology available at the time of reporting. Medical history and current (ongoing) medical conditions, including cancer-related conditions and symptoms will be listed.

2.3.4 Prior antineoplastic therapy

All prior anti-neoplastic therapy will be listed for medication, radiotherapy, surgery and local HCC therapies.

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

The summary of prior anti-neoplastic medications will include the total number of regimens (note: there can be more than one medication per regimen), therapy type at last medication, setting at last medication, time (in days) between end of last medication to start of study treatment, best response at last medication (defined to be the best response during the last treatment regimens recorded), duration (in months) of last response (last response is the response at last medication), reason for discontinuation at last medication and time (in months) from start of last medication to progression. The last medication is defined based on the last end date of all prior regimen components. Prior antineoplastic medications will also be summarized by Anatomical Therapeutic Chemical (ATC) class, and preferred term.

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

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

2.3.5 Diagnosis and extent of cancer

The summary and listing of diagnosis and extent of cancer (disease history) will include primary site of cancer, details of tumor histology/cytology, histological grade, stage at initial diagnosis (only in the listing), stage at time of study entry, time (in months) from initial diagnosis for primary site to start of study treatment, time (in months) since most recent recurrence/relapse or progression to start of study treatment, time (in months) from initial diagnosis of primary site to first recurrence/relapse or progression, current stage of cancer, current extent of disease (metastatic sites), types of lesions (target and non-target lesions) at baseline, and disease burden at baseline for target lesion.

Note: Presence/absence of target and non-target lesions will be based on the data collected on RECIST target/non-target lesion assessment eCRF pages. Metastatic sites will be based on diagnosis page.

2.3.6 Other

All data collected at baseline, including prognostic factors for HCC and Child-pugh Classification Score, will be listed.

2.4 Protocol deviations

The FAS will be used for the protocol deviation summary tables and listings. The number (%) of patients with any CSR-reportable protocol deviation will be tabulated by the deviation category (entry criteria not satisfied; wrong treatment or incorrect dose; developed withdrawal criteria, but not withdrawn; took an excluded concomitant medication; others). The full list of protocol deviations are documented in the Study Specification Document (SSD).

COVID-19 specific protocol deviations will be listed. Details about COVID-19 impact are provided in Section 4.1

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

2.5.1 Study treatment

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

2.5.1.1 Data handling

Imputation rules regarding last and first treatment administration of study drug can be found in Appendix, Section 5.1.1.

2.5.1.2 Duration of exposure to study treatment

Duration of exposure to study treatment is considered by taking into account the duration of exposure to the investigational drug or control, and any combination partner, if applicable:

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 latest of the last dates of exposure to investigational drug (see Table 2-3).

Table 2-3 Definition of last date of exposure of study drug

Study drug	Definition of last date of exposure of study drug
PDR001	The planned end date of the last cycle in which the last non-zero dose of PDR001 was last administered, i.e. the date of PDR001 infusion in the last cycle + 20 days Note: If the patient died or was lost to follow-up before the derived last date of exposure, the last date of exposure to PDR001 for this patient is the date of death or the date of last contact (see Section 2.1.1), respectively. If the derived last date of exposure goes beyond the data cutoff date, it should be truncated to the date of data cutoff.

INC280	Date of last administration of a non-zero dose of INC280.

2.5.1.3 Summary of duration of exposure of investigational drug will include categorical summaries (based on clinically meaningful time intervals) and continuous summaries (i.e. mean, standard deviation, etc.) using appropriate units of time.Cumulative dose

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

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

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

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

For continuous dosing, 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.

2.5.1.4 Dose intensity and relative dose intensity

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

DI (mg/day) = Actual Cumulative dose (mg) / Duration of exposure to study treatment (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 (mg).

Relative dose intensity (RDI) is defined as follows:

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

The duration of exposure of the PDR001 considered for the derivation of the DI and the RDI will be derived from the start date of study treatment (first dosing date) to the last date of exposure to study treatment (see 2.5.1.2), irrespective of date of death, date of last contact and cut-off date.

DI and RDI (including categories: < 0.5, ≥ 0.5 - < 0.75, ≥ 0.75 - < 0.9, ≥ 0.9 - < 1.1 and ≥ 1.1) will be summarized separately for each of the study treatment components, using the duration of exposure of each of the components.

2.5.1.5 Dose reductions, interruptions or permanent discontinuations

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

'Dose changed', 'Dose interrupted', and 'Dose permanently discontinued' fields from the Dosage Administration eCRF pages (DAR) will be used to determine the dose reductions, 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.
Intermediate interruptions that end up in a non-zero dose administration should not be considered dose interruptions.

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 be considered a dose reduction. Only dose change is collected in the eCRF, number of reductions will be derived programmatically based on the change and the direction of the change.

2.5.2 Prior, concomitant and post therapies

Concomitant therapies are defined as any medications (excluding study treatment, prior antineoplastic treatments) and significant non-drug therapies (including physical therapy and blood transfusions) administered in the study and are recorded in the Concomitant Medications/significant non-drug therapies eCRF. These therapies will be coded using the WHO Drug Reference Listing (WHO DRL) dictionary that employs the WHO Anatomical Therapeutic Chemical (WHO ATC) classification system.

Any concomitant therapies starting prior to or after the start of study treatment will be listed.

Imputation rules regarding last and first treatment administration of concomitant therapies can be found in Appendix, Section 5.1.3.

2.5.3 Compliance

Compliance to the study drug is presented by the number of dose reductions, dose interruptions and the percentage of patients who took a predefined percentage (RDI categories: <0.5, 0.5-<0.75, 0.75-<0.9, 0.9-<1.1, ≥1.1) of the number of prescribed doses of study treatment. Details are provided in Section 2.5.1.

2.6 Analysis of the primary objective

Phase Ib part

The primary objective of Phase Ib part is to characterize the safety and tolerability of INC280 in combination with PDR001 and identify the MTD and/or RP2D.

Phase II part

The primary objective of Phase II part is to compare the efficacy of INC280 in combination with PDR001 and PDR001 single agent.

2.6.1 Definition of the primary endpoint

2.6.1.1 Phase Ib part

Safety: Incidence of dose limiting toxicities (DLTs) in the first two cycles of treatment. Incidence and severity of AEs and SAEs, including changes in laboratory values, vital signs and ECGs.

Tolerability: dose interruptions, reductions and dose intensity.

2.6.1.2 Phase II part

Overall response rate (ORR): is defined as the proportion of patients with a best overall response of CR or PR as per Response Evaluation Criteria in Solid Tumors (RECIST v1.1).

2.6.2 Statistical hypothesis, model, and method of analysis

2.6.2.1 Phase Ib part

Safety and tolerability

See Section 2.9 for details in safety analysis.

Identification of a recommended dose

Estimation of the MTD of the treatment will be based upon the estimation of the probability of DLTs in cycles 1 and 2 for patients in the dose determining set (DDS).

A recommended dose below the MTD may be identified based on other safety, clinical, PK, and PD data.

Bayesian adaptive approach

The dose escalation will be guided by a Bayesian analysis of DLT data in cycles 1 and 2 for INC280 and PDR001. The Bayesian analysis will be based on a model with three parts, representing:

- Single agent INC280 toxicity
- Single agent PDR001 toxicity
- Interaction

Single agent toxicity is modelled using logistic regression for the probability of a patient experiencing a DLT against log-dose. The odds of a DLT are then calculated under no interaction for the two single agent toxicities, and interaction is accounted for by adjusting these

odds with an additional model parameter (odds multiplier). Details of the model are given in Appendix 3 of the protocol.

Assessment of patient risk

After each cohort of patients, the posterior distribution for the risk of DLT for new patients at combination doses of interest will be evaluated. The posterior distributions will be summarized to provide the posterior probability that the risk of DLT lies within the following intervals:

Under-dosing:	[0 , 0.16)
Targeted toxicity:	[0.16 , 0.33)
Excessive toxicity:	[0.33 , 1]

The escalation with overdose control (EWOC) principle

Dosing decisions are guided by the escalation with overdose control principal [Rogatko 2007]. A combination dose may only be used for newly enrolled patients if the risk of excessive toxicity at that combination dose is less than 25%.

Prior distributions

A meta-analytic-predictive (MAP) approach was used to derive the prior distribution for the single-agent INC280 and PDR001 model parameters. The MAP prior for the logistic model parameters for this study is the conditional distribution of the parameters given the historical data [Spiegelhalter et al 2004, Neuenschwander et al 2010, Neuenschwander et al 2014]. MAP priors are derived from hierarchical models, which take into account possible differences between the studies.

A full description of the application of the MAP approach to derive the prior distributions of the single agent INC280 and PDR001 model parameters is given in Appendix 3 of the protocol.

The prior distribution for the interaction parameter was based upon prior understanding of possible drug safety interactions. This prior allows for the possibility of either synergistic or antagonistic interaction, and is fully described in Appendix 3 of the protocol.

Starting dose

The starting dose is INC280 200 mg BID and PDR001 300 mg Q3W. For this dose the prior risk of excessive toxicity is 13.9 %, which satisfies the EWOC criterion. A full assessment of the prior risk to patients is given in Appendix 3 of the protocol.

Incorporation of data from ongoing studies

The dose-DLT information generated from the safety patient cohort of INC280 in combination with PD-1 inhibitors in the ongoing study [CEGF816X2201], if available by the time of having dose escalation meetings in this study will be incorporated in the model. A direct down-weighting approach will be used to account for between-trial heterogeneity. Details are provided in Appendix 3 of the protocol.

The following reports will be produced based on the DDS:

- A heatmap of posterior probabilities of DLT rate in the excessive toxicity interval will be presented in the body of the CSR;
- Summary of the DLTs with onset during the evaluation period (dose escalation part only) by primary system organ class, preferred term: recommendations at the time of database lock will be included in the body of the CSR, for each DEM, summary of recommendations will be included in Appendix 16.1.9 of the CSR;
- Listing of inferential results from the BLRM at the time of dabase lock, will be included in Appendix 16.1.9 of the CSR.

2.6.2.2 Phase II part

Estimation of the true ORR in this part of the study will be based upon the observed overall response for patients in FAS, using a Bayesian analysis.

Patients in each group are randomized in a 1:1 ratio into either PDR001+INC280 arm or PDR001 arm. The randomization is stratified by region: Asian vs. non-Asian. The primary efficacy endpoint ORR will be determined per RECIST v1.1 for the primary analysis.

For the primary analysis, a Bayesian logistic regression model with treatment (combination vs. single agent), region (Asian vs. non-Asian), and interaction of treatment and region as covariates will be applied to provide the inference of ORR. Full details of model parameterization and prior specification are provided in Appendix 3 of the protocol. The ORRs of the PDR001+INC280 and PDR001 arms will be compared. If the posterior probability that odds ratio ($ORR_{PDR001+INC280}$ to ORR_{PDR001}) > 1 is greater than 0.8, AND the observed $ORR_{PDR001+INC280}$ is at least 10% greater than the observed ORR_{PDR001}, it will be concluded that the combination treatment has a superior anti-tumor effect compared to the PDR001 single agent treatment.

The posterior mean of ORR adjusted for stratification factor along with 95% credible interval will be provided; the probabilities that the true ORR lies in the following efficacy categories will be reported:

- [0, 20%) no anti-tumor activity
- [20%, 100%] clinically relevant anti-tumor activity.

2.6.3 Handling of missing values/censoring/discontinuations

Patients in the dose escalation part who are ineligible for the DDS will be excluded from the BLRM analysis, although their data will be used for all remaining analyses.

Patients in the phase II part who have BOR of Unknown (UNK) or not assessed (NA) will be considered as a treatment failure in the primary analysis of ORR. Patients with individual scans of UNK or NA will be handled according to RECIST v1.1 (see Appendix 1 of the protocol). The tumor assessement data handling rules in Section 5.1.5 will be applied.

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

2.6.3.1 Supportive analyses

For the phase II, the observed ORR and corresponding 95% exact confidence interval according to Clopper-Pearson method [Clopper and Pearson 1934] will be provided for each study arm overall, and by stratum, if applicable.

The primary analyses on ORR may be repeated using the per-protocol set (PPS), unless FAS and PPS are identical.

2.7 Analysis of key secondary efficacy objective(s)

Not applicable.

2.8 Analysis of secondary efficacy objective(s)

Phase Ib/II parts

The secondary objectives of Phase Ib/II parts are:

- to further characterize the efficacy of INC280 in combination with PDR001 and PDR001 single agent
- To characterize the pharmacokinetic profile of INC280 in combination with PDR001 and PDR001 single agent.
- To assess the pharmacodynamic effect of INC280 in combination with PDR001 and PDR001 single agent in tumor biopsy.

Phase II part

The primary objective of Phase II part is to characterize the safety and tolerability of INC280 in combination with PDR001 and PDR001 single agent.

2.8.1 Definition of secondary endpoints

2.8.1.1 Phase I/II parts

2.8.1.1.1 Efficacy of INC280 in combination with PDR001 and PDR001 single agent

The BOR, TTP, PFS, DOR, TTR and OS will be analyzed using FAS to characterize the efficacy of PDR001+INC280 and PDR001 single agent in the phase Ib part and phase II part. Tumor response related endpoints will be analyzed based on the local Investigator assessments according to RECIST 1.1 and irRC, respectively.

Definitions of the relevant endpoints is given below:

- **Best Overall Response (BOR):** is defined as the best response recorded from the start of the study treatment until disease progression/recurrence as defined for RECIST v1.1 and irRC. Complete and partial responses must be confirmed by repeat assessments that should be performed not less than 4 weeks after the criteria for response are first met. Additionally, for irRC, progressive disease should be confirmed in a similar manner.
- **Overall Response Rate (ORR):** see Section 2.6.1.2.
- **Time to progression (TTP):**

- For RECIST v1.1, TTP is defined as the time from the date of randomization/start of treatment to the date of the first documented progression per RECIST v1.1 or death due to underlying cancer ("study indication" – see Section 5.1.4).
- For irRC, TTP is defined as the time from the date of randomization/start of treatment to the date of the first documented and confirmed progression per irRC or death due to underlying cancer ("study indication" – see Section 5.1.4).

  Progressive disease should be confirmed by a repeat assessment that should be performed not less than 4 weeks after the criteria for progression are first met. The date of progression will then be the date of the first of these two assessments.
  For patients without a confirmation assessment, and with no subsequent assessments of SD, or better, a single assessment will be used as date of progression.

  If a patient has not experienced an event at the time of the analysis or has started a new anticancer therapy, TTP will be censored at the date of the last adequate tumor evaluation before the start of a new anticancer therapy, if any.

- **Progression-free Survival (PFS):**
  - For RECIST v1.1, PFS is defined as the time from the date of randomization/start of treatment to the date of the first documented progression per RECIST v1.1 or death due to any cause.
  - For irRC, PFS is defined as the time from the date of randomization/start of treatment to the date of the first documented and confirmed progression per irRC or death due to any cause.

    Progressive disease should be confirmed by a repeat assessment that should be performed not less than 4 weeks after the criteria for progression are first met. The date of progression will then be the date of the first of these two assessments.
    For patients without a confirmation assessment, and with no subsequent assessments of SD, or better, a single assessment will be used as date of progression.

    If a patient has not experienced an event at the time of the analysis or has started a new anticancer therapy, PFS will be censored at the date of the last adequate tumor evaluation before the start of a new anticancer therapy, if any.
- **Duration of Response (DOR):** is defined for responder as the time between the date of first documented response (CR or PR) and the date of first documented progression or death due to any cause.
  DOR applies only to patients with a BOR of confirmed CR or PR (RECIST v1.1).
  For irRC, DOR is similarly defined for confirmed irCR or irPR patients.

  If progression or death due to any cause has not occurred or patient has started a new anticancer therapy, then the patient is censored at the date of last adequate tumor assessment before the start of a new anticancer therapy, if any.
- **Time to Response (TTR):** is defined as the time from the date of randomization/start of treatment to the date of first documented response (CR or PR, which must be confirmed subsequently) for patients who achieved a confirmed CR or PR. All patients in the FAS will be included in TTR calculations.

Patients who did not achieve a confirmed CR or PR will be censored at the maximum follow-up time for patients who had a PFS event (i.e. either progressed or died due to any cause), or at the date of last adequate tumor assessment before the start of a new anticancer therapy (if any) otherwise.

For irRC, TTR is similarly defined for confirmed irCR or irPR patients.

- **Overall Survival (OS):** is defined as the time from date of randomization/start of treatment to date of death due to any cause.

  If a patient is not known to have died, OS time will be censored at the date of last contact.

2.8.1.1.2 Pharmacokinetic profile of INC280 in combination with PDR001 and PDR001 single agent

See Section 2.10

2.8.1.1.3 Pharmacodynamic effect of INC280 in combination with PDR001 and DR001 single agent in tumor biopsy

See Section 2.14.

2.8.1.2 Phase II part

Safety: Incidence and severity of AEs and SAEs, including changes in laboratory values, vital signs and ECGs.

Tolerability: dose interruptions, reductions and dose intensity

2.8.2 Statistical hypothesis, model, and method of analysis

Tumor response related endpoints will be analyzed based on the local Investigator assessments according to RECIST 1.1 and irRC, respectively.

Individual lesion measurements and overall response assessments will be listed by patient and assessment date. BOR, TTP, PFS, DOR, TTR and OS will be listed by patient. The following summaries and analyses will be performed for the phase Ib by treatment group (if at least 10 patients in a treatment group) and for the phase II part by study treatment where applicable:

- BOR is the best response recorded from the start of the treatment until disease progression/recurrence. However, any assessments taken more than 30 days after the last dose of study therapy will not be included in the BOR derivation. Moreover, if any alternative cancer therapy is taken while on study, any subsequent assessments will be excluded from the BOR determination.

  ORR 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.
- For TTP, TTR, PFS and OS, a Kaplan-Meier plot will be presented. Median time-to-event values (in months) with corresponding 95% CI, 25th and 75th percentiles (Brookmeyer and Crowley 1982, Klein and Moeschberger 1997) and Kaplan-Meier estimated probabilities (time to event free rates) with corresponding 95% CIs (Greenwood's formula, Kalbfleisch and Prentice 1980) at several time points (3, 6, 12, 18 and 24 months) will be presented.

The number (%) and type of events per endpoint and patients censored will also be summarized

- DOR will be listed for all patients with a response. Summaries of DOR may be provided if a sufficient number of patients responded.

For PK see Section 2.10

For PD see Section 2.14.

For safety endpoints see section 2.9.

2.8.3 Handling of missing values/censoring/discontinuation

Patients who have BOR of Unknown (UNK) or not assessed (NA) will be considered as a treatment failure in the primary analysis of ORR. Patients with individual scans of UNK or NA will be handled according to RECIST v1.1 (see Appendix 1 of the protocol) and irRC (see Appendix 2 of the protocol). If any new anticancer therapy is taken while on study, any subsequent assessments will be excluded from the BOR determination.

For the analysis of TTP, patients without documented disease progression or death due to underlying cancer ("study indication" – see Section 5.1.4) will be censored at the time of last adequate tumor assessment documenting non-progression (one of CR, PR, SD) before the start of a new anticancer therapy, if any. Patients without any valid post-baseline tumor assessment response (one of CR, PR, SD, or PD) will be censored on the date of randomization/start date of treatment. Patients who have a PFS event (progression or death due to any cause) after two or more consecutive missing assessments from the last valid tumor assessment will be censored on the last valid tumor assessment (or on the start date of treatment among those without a postbaseline tumor assessment).

For the analysis of PFS, patients without documented disease progression or death due to any cause will be censored at the time of last adequate tumor assessment documenting non-progression (one of CR, PR, SD) before the start of a new anticancer therapy, if any. Patients without any valid post-baseline tumor assessment response (one of CR, PR, SD, or PD) will be censored on the date of randomization/start date of treatment. Patients who have a PFS event (progression or death due to any cause) after two or more consecutive missing assessments from the last valid tumor assessment will be censored on the last valid tumor assessment (or on the start date of treatment among those without a postbaseline tumor assessment).

For the analysis of DOR, patient without documented disease progression or death due to any cause will be censored at the date of last adequate tumor assessment documenting non-progression (one of CR, PR, SD) before the start of a new anticancer therapy, if any.
DOR apply only to patients with a BOR of confirmed CR or PR (RECIST v1.1) or of confirmed irCR or irPR (irRC).

For the analysis of TTR, patients without confirmed CR or PR will be censored at the maximum follow-up time for patients who had a PFS event (i.e. either progressed or died due to any cause), or at the date of last adequate tumor assessment before the start of a new anticancer therapy (if any) otherwise. All patients in the FAS will be included in TTR calculations.

For the analysis of OS, patient without an event (death) will be censored at the date of last contact.

Other missing data will simply be noted as missing on appropriate tables/listing.

2.9 Safety analyses

The assessment of safety is based on the type and frequency of Adverse Events (AEs) as well as on the number of laboratory values that fall outside of pre-determined ranges (Common Toxicity Criteria for Adverse Events (CTCAE) grading limits or normal ranges as appropriate). Other safety data include electrocardiogram and vital signs.

The Safety set will be used for summaries and listings of safety data with the exception of dose limiting toxicities (DLTs) for which the DDS will be used.

For all safety reporting the overall observation period and safety summaries will follow the instructions mentioned in section 2.1.1**Error! Reference source not found.**.

2.9.1 Adverse events (AEs)

2.9.1.1 Data handling

Adverse events will be coded using the latest available version of the MedDRA and assessed according to the CTCAE version 4.03. If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening, corresponding to Grades 1 - 4, will be used. CTCAE Grade 5 (death) will not be used in this study (but is collected as a seriousness criterion); rather, information about deaths will be collected through a Death form.

2.9.1.2 Data analysis

Adverse Events Summaries

AE summaries will include all AEs occurring during the on-treatment period. All AEs collected in the AE eCRF page will be listed along with the information collected on those AEs e.g. AE relationship to study drug, AE outcome etc. AEs with start date outside of on-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 primary system organ class will be presented alphabetically and the preferred terms will be sorted within primary SOC in descending frequency. The sort order for the preferred term will be based on their frequency in the investigational arm

The following AE summaries will be produced by treatment:

- Overview of adverse events and deaths (number and % of patients who died, with any AE, any SAE, any dose reductions/interruptions, AE leading to discontinuation)
- AEs by SOC and PT, summarized by relationship (all AEs and AEs related to study treatment);
- Seriousness (SAEs and non-SAEs)
- Leading to treatment discontinuation
- Leading to dose interruption/adjustment
- Requiring additional therapy
- Leading to fatal outcome
- Dose limiting toxicities by PT

The following listings will be produced:

- All adverse events (safety set)
- Adverse events among patients who were not treated (all screened patients)

Deaths

Separate summaries for on-treatment and all deaths (including post-treatment death) will be produced by treatment arm, system organ class and preferred term.

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

EudraCT and clinicaltrials.gov requirements for AEs and Deaths summaries

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

2.9.2 Adverse events of special interest

An adverse event of special interest is a grouping of adverse events that are of scientific and medical concern specific to compound PDR001 and INC280. These groupings are defined using

MedDRA terms, SMQs (standardized MedDRA queries), HGLTs (high level group terms), HLT (high level terms) and PTs (preferred terms). Customized SMQs (Novartis MedDRA queries, NMQ) may also be used. A NMQ is a customized group of search terms which defines a medical concept for which there is no official SMQ available or the available SMQ does not completely fit the need. It may include a combination of single terms and/or an existing SMQ, narrow or broad. For each specified AESI, number and percentage of subjects with at least one event of the AESI occurring during on-treatment period will be summarized for each study drug separately:

- All AESIs
- AESIs suspected to be study drug related
- Serious AESIs
- AESIs leading to study drug discontinuation
- AESIs leading to dose adjustment or study drug interruption
- AESIs leading to fatal outcome

All AESIs will be listed for each study drug separately. In addition, a listing of all grouping levels down to the MedDRA preferred terms used to define each AESI will be provided for each study drug.

2.9.3 Laboratory data

2.9.3.1 CTC grading for laboratory parameters

Laboratory data will be converted into SI units and classified (by Novartis statistical programming) into CTC grades according to CTCAE version 4.03. The calculation of laboratory CTC grades will be based on the observed laboratory values only, clinical assessments will not be taken into account. The criteria to assign CTC grades are given in Novartis internal criteria for CTC grading of laboratory parameters. The latest available version of the document based on the underlying CTCAE version 4.03 at the time of analysis will be used.

For laboratory tests where grades are not defined by CTCAE version 4.03, results will be graded by the low/normal/high (or other project-specific ranges, if more suitable) classifications based on laboratory normal ranges.

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

2.9.3.2 Imputation rules

See Section 5.3.

2.9.3.3 Data analysis

On analyzing laboratory, data from all sources (central and local laboratories) will be combined. The summaries will include all assessments available for the lab parameter collected prior to the end date of the on-treatment period (see section 2.1.1.6).

The following summaries will be produced separately for hematology, coagulation, urinary and biochemistry parameters (by laboratory parameter and treatment):

- Worst post-baseline CTC grade (regardless of the baseline status). Each will be counted only for the worst grade observed post-baseline;
- Shift tables using CTC grades to compare baseline to the worst on-treatment value;
- For laboratory tests where CTC grades are not defined, shift tables using the low/normal/high/(low and high) classification to compare baseline to the worst on-treatment value.

The following listings will be produced for the laboratory data:

- Listing of all CTC grade 3 or 4 laboratory toxicities

All scheduled/unscheduled assessments should be assigned to time windows. In case of multiple values per window, the one closest to the planned visit date should be used. If 2 values are equidistant to the planned visit date, the selection should be made by selecting the one assessed by central (if any) and otherwise - for multiple central assessments - the last value.

Refer to Section 7.2.2 of the protocol for all laboratory parameters that will be summarized.

Liver function parameters

Liver function parameters of interest are total bilirubin (TBL), ALT, AST and alkaline phosphatase (ALP). The number (%) of patients with worst post-baseline values as per Novartis Liver Toxicity guidelines will be summarized.

The following summaries will be produced:

- ALT or AST > 3xULN
- ALT or AST > 5xULN
- ALT or AST > 8xULN
- ALT or AST > 10xULN
- ALT or AST > 20xULN
- TBL > 2xULN
- TBL > 3xULN
- ALT or AST > 3xULN & TBL > 2xULN
- ALT or AST > 3xULN & TBL > 2xULN & ALP < 2xULN

Potential Hy's Law events are defined as those s with concurrent occurrence of AST or ALT > 3xULN and TBL > 2xULN and ALP < 2xULN in the same assessment sample during the on-

treatment period. Further medical review has to be conducted to assess potential confounding factor such as, liver metastases, liver function at baseline etc.

Renal function parameters

Renal function parameters of interest are Creatinine, Urea or Blood Urea Nitrogen (BUN) and the macroscopic panel (dipstick) for Bilirubin, Blood, Glucose, Ketones, pH, Protein, Specific Gravity, White Blood Cells .

2.9.4 Other safety data

2.9.4.1 ECG and cardiac imaging data

As described in Section **Error! Reference source not found.**, baseline is the last available and valid assessment performed or value measured on or before the date of first administration of study treatment. Especially for ECG, where study requires multiple replicates per timepoint, the average of all these available ECG measurements associated with the baseline assessment will be calculated. Scheduled study day 1 pre-dose ECGs will be considered to have been obtained prior to study drug administration if dosing time is missing.

Triplicate ECGs will be done at all timepoints. The average of all available measurements associated with the nominal time point will be used for the analyses. If a patient has more than one ECG assessment associated with a specific post-baseline pre-dose timepoint, the one before and closest to the planned timepoint should be used. Scheduled pre-dose ECGs will be considered to have been obtained prior to study drug administration if dosing time is missing.

For the other timepoints, if a patient has more than one associated assessment, the one closest to the planned timepoint should be used; if two assessments are equidistant to the planned timepoint, the last assessment associated with the nominal time point will be used for the analyses.

A standard 12 lead ECG including PR, QRS, QT, QTcF, QTcB and HR intervals will be obtained locally and independently reviewed by a central laboratory.

The number and percentage of patients with notable ECG values will be presented by treatment group. ECG values considered notably abnormal are defined in Table 2-4.

Table 2-4 Criteria for notable ECG values

ECG parameter	Criteria for notable ECG values
QT, QTcF, QTcB (ms)	○ New value of > 450 and ≤ 480 ms ○ New value of > 480 and ≤ 500 ms ○ New value of > 500 ms ○ Increase from baseline of > 30 ms to ≤ 60 ms ○ Increase from baseline of > 60 ms
HR (bpm)	○ Increase from baseline >25% and to a value >100 bpm ○ Decrease from baseline >25% and to a value <50 bpm
PR (ms)	○ New PR >200 ms ○ Increase from baseline >25% and to a value >200 ms
QRS (ms)	○ New QRS >120 ms

	○ Increase from baseline >25% and to a value >120 ms

A listing of all ECG assessments will be produced by treatment arm and notable values will be flagged. In the listing, the assessments collected during the post-treatment period will be flagged.

2.9.4.2 Vital signs

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

Vital signs collected during on-treatment will be summarized. The number and percentage of patients with notable vital sign values (high/low) will be presented by treatment group. Vital sign values considered notably abnormal are defined in Table 2-5.

Table 2-5 Clinically notable changes in vital signs

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

A listing of all vital signs will be produced by treatment arm and notable values will be flagged. In the listing, the assessments collected during the post-treatment period will be flagged.

2.9.4.3 Tolerability

Tolerability of study treatment will be assessed by summarizing the number of dose interruptions and dose reductions by treatment group. Reasons for dose interruption and dose reductions will be listed by patient and treatment group and summarized by treatment group. Cumulative dose, dose intensity and relative dose intensity of study treatment (see Section 2.5) will be also be used to assess tolerability.

2.10 Pharmacokinetics analyses

All PK analyses will be performed for INC280, CMN288 and PDR001 based on the PAS.

PK parameters will be calculated using non-compartmental methods using Phoenix WinNonlin version 6.4 or later (Pharsight, Mountain View, CA).

PK parameters shown in Table 2-6 will be summarized and reported for each analyte. AUClast, AUCtau, Cmax, and Tmax are the primary PK parameters. AUCtau will be AUC0-12h for INC280 and CMN288, and AUC0-504h for PDR001. Other parameters, including AUCinf

(Cycle 1 Day 1 only), T1/2, CL， Racc and Vz are considered secondary parameters for PDR001 only.

Table 2-6 Non-compartmental PK parameters

PK parameter	Description
AUClast	The area under the curve (AUC) from time zero to the last measurable analyte (INC280, CMN288 or PDR001) concentration sampling time (tlast) (mass x time x volume-1)
AUCtau[1]	The AUC calculated to the end of a dosing interval (tau) at steady-state (mass x time x volume-1)
AUCinf [2]	The AUC from time zero to infinity (mass x time x volume-1)
Tmax	The time to reach maximum (peak) analyte concentration after study drug dose administration (time)
Cmax	The maximum (peak) observed plasma, blood, serum, or other body fluid analyte concentration after study drug administration (mass x volume-1)
T1/2 [3]	Elimination half-life
CL [3]	The total body clearance of drug from the plasma (volume x time-1)
Racc[3]	Accumulation ratio calculated as AUCtau at Cycle 3/AUCtau at Cycle 1
Vz [3]	The volume of distribution during the terminal elimination phase

[1] AUCtau will be AUC0-12h for INC280 and CMN288, and AUC0-504h for PDR001.

[2] AUCinf is for PDR001 at Cycle 1 Day 1 only

[3] PDR001 only

2.10.1 Data handling principles

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

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

2.10.2 Data analysis set

All PK analyses and PK summary statistics will be based on the PAS. Only PK blood samples with date and time and for which the last prior dose dates and times are adequately recorded will be included in the PK analyses.Patient data may be removed on an individual basis.

2.10.3 Basic tables, figures and listing

All individual plasma drug concentration data will be listed by treatment group, visit, and timepoint.

Descriptive statistics will be presented for all pharmacokinetic parameters, as described in Table 2-7.

Table 2-7 Descriptive analysis

Parameters	Descriptive statistics
AUC(1), C_{max}, CL, Vz, R_{acc}, $T_{1/2}$	Mean standard deviation, CV% mean, geometric mean, CV% geo-mean, median, minimum, and maximum.
T_{max}	Median, minimum, and maximum.

(1) Includes all AUC parameters
CV% = coefficient of variation (%) = sd/mean*100
CV% geo-mean = sqrt (exp (variance for log transformed data)-1)*100

Zero concentrations will not be included in the geometric mean calculations. Tmax will be summarized in terms of median values and ranges. Missing concentrations or PK parameter values will not be imputed. A listing of derived PK parameters per patient will be produced by treatment group.

Analysis of drug concentrations

Descriptive statistics for drug concentrations, including n, m (number of non-zero concentrations), arithmetic mean, CV% mean, SD, median, geometric mean, CV% geo-mean, minimum and maximum, will be presented at each scheduled time point by treatment. Zero concentrations will not be included in the geometric mean calculation.

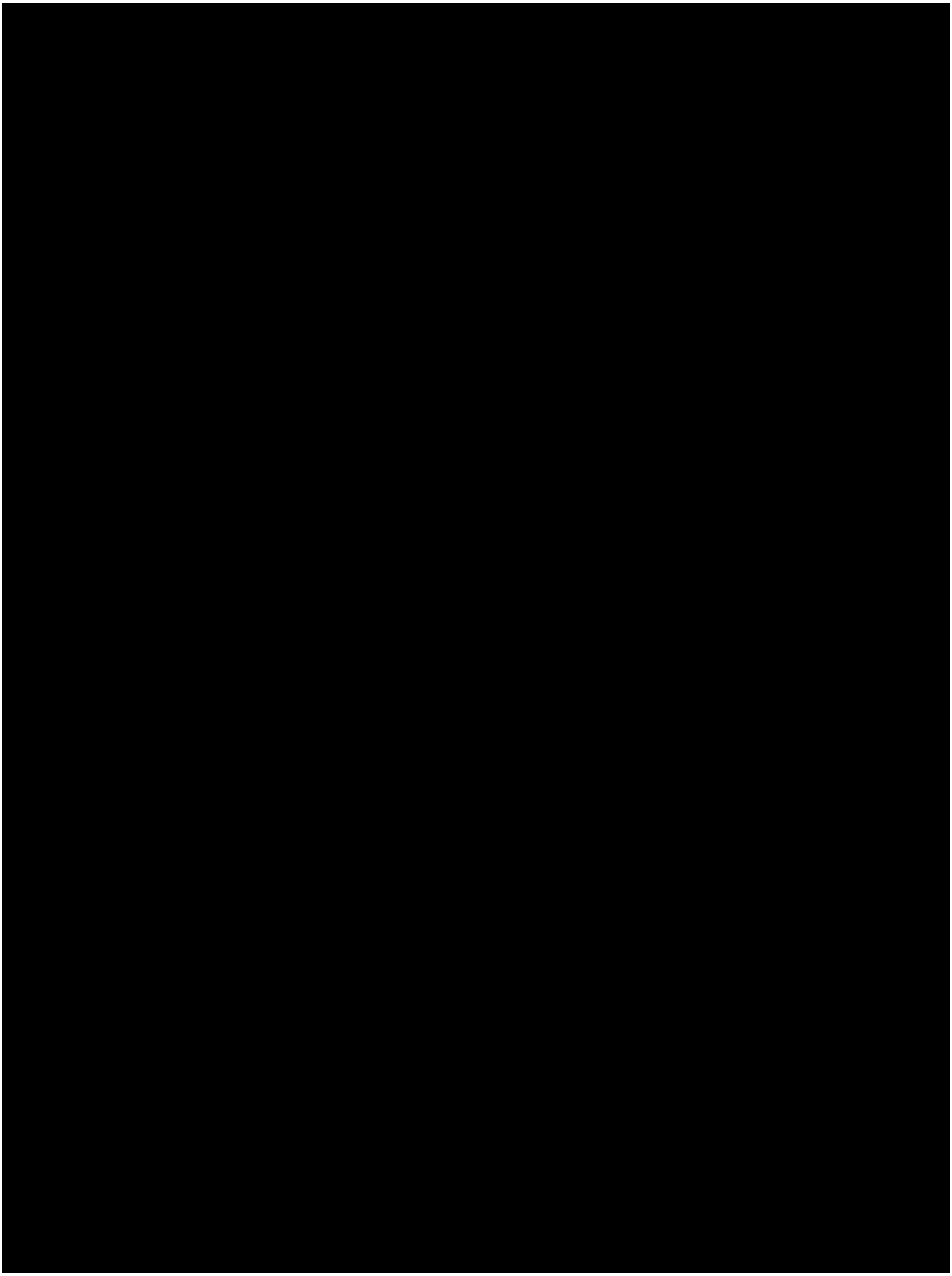
The mean (+/- SD) and geometric mean concentration-time profiles by treatment over time will be displayed graphically on the linear and semi-log view, for phase Ib only (Cycle 2 Day 1 for INC280 and CMN288, Cycle 1 Day 1 and Cycle 3 Day 1 for PDR001).

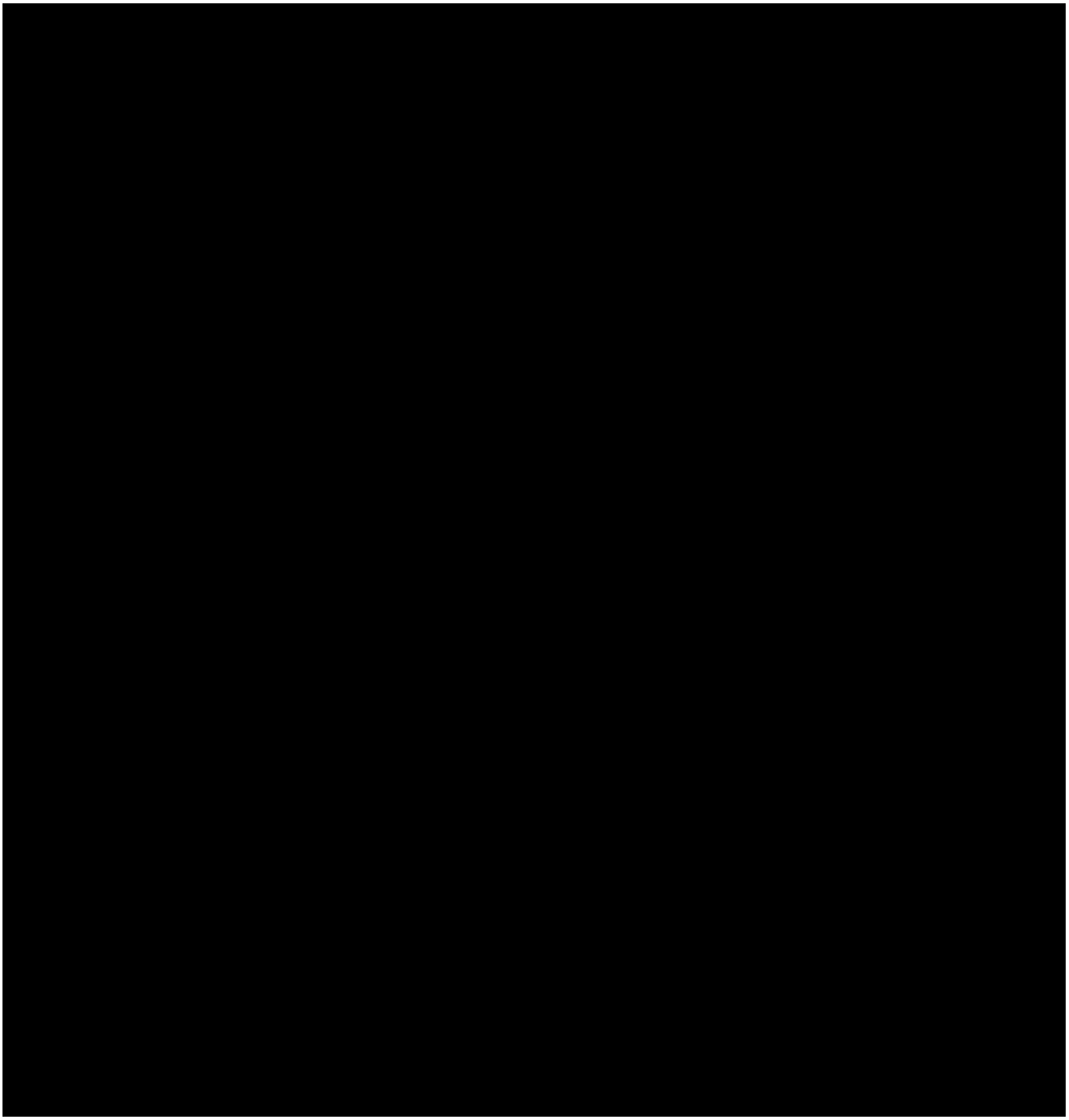
2.11 PD and PK/PD analyses

The objective is to assess the pharmacodynamic effect of INC280 in combination with PDR001 and PDR001 single agent in tumor biopsy.

The FAS will be used for all biomarker analysis. The expression of the pharmacodynamic markers, including CD8 (TIL) and PD-L1 (tumor cells), will be assessed using paired tumor samples at screening/baseline and on-treatment.

Assessments at screening/baseline and on-treatment and change from baseline of the biomarker levels will be listed by patient and summarized (when sample size is sufficient) by treatment group using descriptive statistics.





2.13 Patient-reported outcomes

Not Applicable.

Table 2-8 List of biomarkers evaluated and the collection time points

Sample Type	Visit/ Time point	Volume	Marker*	Purpose
Tumor samples				
Newly obtained tumor sample	Screening (recommended to be collected at least 2 weeks after the last dose of sorafenib)	Newly obtained formalin fixed tumor sample in ethanol (3-6 passes)	[redacted]	[redacted]
	6-9 weeks after start of study treatment		Expression by IHC (e.g., CD8, PD-L1, [redacted])	Pharmacodynamic (PD) markers
			[redacted]	[redacted]
	At progression of disease only for patients who had a response as per investigator assessment (optional)		[redacted]	[redacted]
[redacted]				

Note: On days and time points when biomarker and pharmacokinetic blood samples are being collected, thePK sample must be drawn first.

2.14.5 Exploratory Data analyses

If deemed necessary, this part of analysis may be described in separate analysis plan documentation and displayed external to the main study CSR.

[redacted]

2.16 Interim analysis

No formal interim analyses was planned.

3 Sample size calculation

3.1 Phase Ib part

Cohorts of 3 to 6 evaluable patients will be enrolled in the dose-escalation part including at least six patients at the MTD/RP2D level, as described in Section 6.2.3 of the protocol. Multiple cohorts may be sequentially enrolled to the same dose level. Additional cohorts of 1 to 6 patients may be enrolled at any dose level below the estimated MTD/RP2D for further elaboration of safety and pharmacokinetic parameters as required. At least 12 patients are expected to be in the dose escalation part. If a recommended phase II dose is identified without determination of the MTD, fewer than 12 patients may be required.

3.2 Phase II part

Sample size is considered for assessment of ORR. *A priori* the true mean of ORR is assumed to be 20% in both cMET high and cMET low patient groups treated with PDR001 single agent. It is assumed that the combination with INC280 will improve the mean of ORR to 40%. A minimally informative unimodal [Neuenschwander et al 2008] beta prior distribution with mean as assumed is then specified as following:

- PDR001+INC280: $ORR_{PDR001+INC280} \sim Beta(0.67,1)$
- PDR001: $ORR_{PDR001} \sim Beta(0.25,1)$

The ORR of the PDR001 in combination with INC280 treatment will be compared to that of the PDR001 single agent treatment. A Bayesian logistic regression model will be used to perform this comparison. The full model will include a covariate for treatment effect, and will also explore region effects, and treatment/region interaction. Here, operating characteristics are described under the assumption that there is no region effect, and a simplified logistic regression model including only treatment as a covariate is used to provide inference.

Given 30 patients in each treatment, and under the assumption of 20% ORR for PDR001 single agent, the probabilities of success under different assumed scenarios of true ORRs for the combination are presented in Table 3-1.

- For true ORRs for combination and single agent treatment, of 40% and 20%, respectively, the probability to declare superior anti-tumor effect of the combination treatment is 78.5%.
- If the true ORRs of combination and single agent treatment in patients are both 20%, the probability to incorrectly declare superior anti-tumor effect of the combination treatment is 14.1%.

Table 3-1Operating characteristics for $ORR_{PDR001+INC280}$ vs. ORR_{PDR001} comparison

True ORR_{PDR001}	True $ORR_{PDR001+INC280}$	Probability of success (success when Posterior P(Odds($ORR_{PDR001+INC280}$)/Odds(ORR_{PDR001})>1)>0.80)) & (Observed $ORR_{PDR001+INC280}$ – observed ORR_{PDR001}) > 10%)
20%	10%	0.008
	20%	0.141
	30%	0.433
	40%	0.785
	50%	0.955

4 Change to protocol specified analyses

In the analysis of vital signs, "shift table baseline to worst on-treatment result" specified in (see Section 10.5.3.4 of the protocol) will not be produced. Instead, "number (%) of patients having on treatment notable vital sign values" will be provided (see Section 2.9.4.2).Definition of the per-protocol analysis set was updated, as this was considered more relevant by the study team.

[redacted]

BOR will be summarized using the 95% exact confidence interval and not the 90% described in the protocol. Given that 95% confidence intervals will presented in the entire CSR, the selection of a 90% only in this case has no reasoning.

Definitions of DOR and TTR were updated in order to be alligned with other relevant studies of the same compound.

Various minor changes were applied in the analysis described in the protocol, as considered appropriate by the study team.

All changes were defined in the statistical analysis plan before the data base lock.

4.1 Planned analysis due to COVID-19

The COVID-19 pandemic had minimal impact on this study because at the start of the pandemic, the vast majority of subjects had discontinued the study treatment and completed the safety follow-up phase. COVID-19 specific protocol deviations will be listed.

5 Appendix

5.1 Imputation rules

5.1.1 Study drug

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

Scenario 1: If the dose end date is completely missing and there is no EOT page and no death date, the patient is considered as on-going:

The patient should be treated as on-going and the cut-off date should be used as the dose end date.

Scenario 2: If the dose end date is completely or partially missing and the EOT page is available:

Case 1: The dose end date is completely missing, and the EOT completion 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 dose end date, and yyyy = the year of EOT date and mm < the month of EOT date:

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 start date of treatment, if the imputed date is < start date of treatment:

Use the treatment start date

Patients with missing start dates are to be considered missing for all study treatment component related calculations and no imputation will be made. If start date is missing then end-date should not be imputed.

5.1.2 AE date imputaition

A missing AE start date will be imputed using the following logic matrix described in **Error! Reference source not found.**.

Table 5-1 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 5-2 is the legend to the logic matrix shown in **Error! Reference source not found.** and details the relationship of AE start date to study treatment start date.

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

	AE start date relationship	Imputation
(A)	After treatment start	01MONYYYY
(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.

5.1.3 Concomitant medication date imputation

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

5.1.3.1 Prior therapies date imputation

Start date

The same rule which is applied to the imputation of AE/concomitant medication start date (see Section **Error! Reference source not found.**) will be used, with the exception that TRTSTD-1 will be used instead of TRTSTD+1.

End date

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

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

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

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

5.1.3.2 Post therapies date imputation

Start date

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

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

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

End date

No imputation.

5.1.4 Deaths

Due to the fact that the reason of death is inserted as a free text into the database, a wider categorization should be applied in order to be able to distinguish the cases where a death is considered an event for the endpoints TTP and DOR (namely deaths due to study indication). For this wider categorization, the preferred term of the primary reason of death will be used.

The two basic categories will be the following ones:

- "Study indication": for all cases where death is due to underlying cancer. This category will include the cases with following preferred terms:
  - Disease progression
  - Hepatocellular carcinoma
- "Other": for all other cases where death is not due to underlying cancer.

Regarding incomplete death dates, the following imputation rules will be used:

- When only the day of death is missing, then
  death date=max [(01-MMM-YYYY), min (last contact date + 1, cut-off date)].
- When day and month of death is missing, then
  death date=max[(01-JAN-YYYY, min (last contact date + 1, cut-off date)].

The imputed dates will not appear in the listings

5.1.5 Other imputations

For date of diagnosis and date of previous progression, when recorded as a partial date, the missing day is imputed to the 1st of the month (e.g., DEC2007 imputed to 01DEC2007), and if the day and month are both missing then to 1st of January of that year (e.g., 2007 imputed to 01JAN2007). Such imputed data will not appear in the listings.

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

In case there is an entry with a date completely missing (e.g. in tumor assessments, in prior therapies, in post-treatment therapies, etc.), no imputation will be performed and the entry will be ignored.

5.2 AEs coding/grading

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

AEs will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 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). Grade 5 (death) will not be used in this study.

5.3 Laboratory parameters derivations

Imputation Rules

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

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

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

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

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

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

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

CTC grades for the derived absolute WBC differential counts (neutrophils, lymphocytes) and corrected calcium will be assigned as described above for grading.

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

See section 2.2.2.

5.6 Confidence interval for response rate

Responses will be summarized in terms of percentage rates with 100(1 − α)% confidence interval using exact binomial confidence interval (implemented using SAS procedure FREQ with EXACT statement for one-way table [Clopper and Pearson 1934].

5.7 Waterfall graphs

Waterfall graphs will be used to depict anti-tumor activity. These plots will display the best percentage change from baseline in the sum of diameters of target lesions for each patient.

Note: Patients without any valid assessments to calculate a percentage change from baseline value will be excluded from the graphs. Assessments with an unknown overall response will be included as long as the sum of diameters of target lesions is correctly computed on the same lesions assessed at baseline.

Patients will be ordered in the graph from left (worst change) to right (best change).

1. Bars above the horizontal axis (0%) representing tumor growth,

2. Bars under the horizontal axis (0%) representing tumor shrinkage.

A special symbol (e.g. ∗) will be added below the bottom of respective bars for confirmed RECIST response (CR or PR), with corresponding specificatons in footnote. The total number of patients displayed in the graph (n) over the total number of patients in the FAS (N) will be shown. The BOR will be shown above each of the displayed bars in the graph. Symbols will be used to differentiate groups of interest, i.e. treatment group. A horizontal threshold line at -30% will be shown.

5.8 Kaplan-Meier estimates

An estimate of the survival function in each patient group will be constructed using Kaplan-Meier (product-limit) method as implemented in PROC LIFETEST with METHOD=KM option. The PROC LIFETEST statement will use the option CONFTYPE=LOGLOG.

Median survival for each treatment group will be obtained along with 90% confidence intervals calculated from PROC LIFETEST output using the method of [Brookmeyer and Crowley 1982]. Kaplan-Meier estimates of the survival function with 90% confidence intervals at specific time points will be summarized. The standard error of the Kaplan-Meier estimate will be calculated using Greenwood's formula [Collett 1994].

6 Reference

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